Universidade de Lisboa

Faculdade de Farmácia

Systematic Review of Pharmacoeconomic Studies on Immuno-Oncology

Assessment of the cost-effectiveness of Immuno-oncology medicines used in the treatment of Advanced Melanoma

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Mestrado Integrado em Ciências Farmacêuticas

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Trabalho de campo do Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

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RESUMO

A imunoterapia para o cancro mudou o paradigma de tratamento para todas as pessoas diagnosticadas com Melanoma Metastático. Estas imunoterapias quando comparadas com a quimioterapia, proporcionam aos doentes não só um aumento na sua esperança de vida mas também uma melhoria muito significativa na sua qualidade de vida. No entanto, esta nova abordagem acarreta um aumento nos custos relacionados com o tratamento e tem particularidades no que concerne à avaliação da sua eficácia clínica.

Num ambiente definido pela escassez de recursos é crucial definir quais as formas mais eficazes de tratar as doenças. Por essa razão, os decisores devem suportar as suas decisões nos estudos económicos, porque ao considerarem todo o impacto económico causado por novos tratamentos podem assegurar a sustentabilidade dos sistemas de saúde.

O objetivo deste estudo é rever, sistematizar e avaliar os estudos de custo-efetividade relevantes relacionados com o uso de imunoterapia para o tratamento do Melanoma Metastático produzidos desde 2013.

Foi realizada um revisão sistemática da literatura para estudos de custo-efetividade e custo-utilidade de imunoterapias para o cancro. No total 480 estudos foram triados, desses estudos, 9 reuniam todos os critérios de inclusão. A avaliação da qualidade dos estudos incluídos foi realizada com recurso a uma ferramenta validada, “Quality of Health Economic Studies” ou QHES.

Dois dos estudos incluídos avaliaram a relação de custo-efetividade do Pembrolizumab comparada com o Ipilimumab. Outros dois estudos avaliaram a relação de custo-efetividade do Nivolumab comparada com a do Ipilimumab. Dois estudos avaliaram a relação de custo-efetividade de diferentes abordagem sequenciais no tratamento de doentes sem mutações BRAF. Dois estudos estudaram a relção de custo-efetividade de diferentes combinações terapêuticas. Um desses estudos avaliou a relação de custo-efetividade da combinação de Talimogene Laherparepvec com Ipilimumab em comparação com Ipilimumab em monoterapia. Outro estudo avaliou a relação de custo-efetividade da combinação de Nivolumab com Ipilimumab em comparação com Ipilimumab em monoterapia. Por fim, um estudo avaliou a relação de custo-efetividade de Vemurafenib seguido de Ipilimumab como segunda linha de tratamento em comparação com Vemurafenib em monoterapia.

O questionário QHES revelou que seis dos noves estudos incluídos eram de alta qualidade e que os restantes três, apesar de terem uma qualidade aceitável, ficaram perto do limiar de alta qualidade.

PALAVRAS-CHAVE: Melanoma; Revisão Sistemática; Imunoterapia; Cancro; Custo-efetividade

ABSTRACT

Cancer immunotherapies have given new hopes to patients with Metastatic Melanoma by improving the overall survival and the quality of life of the patients when compared with conventional chemotherapy. However, these new therapies increase the costs of treatment and present new challenges regarding their clinical efficacy assessment. In an environment defined by the scarcity of resources, it is crucial to define the most effective ways of managing diseases. Therefore, decision-makers must support their decisions on economic analysis in order to consider the economic impact of new treatments and in this way, ensure the sustainability of health care systems.

The purpose of this study is to review, systematize and assess the relevant cost-effectiveness studies produced since 2013 regarding cancer immunotherapies for Metastatic Melanoma.

A systematic literature review was conducted for cost-effectiveness and cost-utility, analysis of cancer immunotherapy drugs. A total of 480 studies were screened and, of those, nine studies met all the inclusion criteria. The quality of the included studies was evaluated with the Quality of Health Economic Studies (QHES) assessment tool.

Two studies assessed the cost-effectiveness (CE) of Pembrolizumab against Ipilimumab. Another two studies analysed the CE of Nivolumab against Ipilimumab. Two studies assessed the cost-effectiveness of different sequential approaches for the treatment of BRAF wild-type patients. Two studies measured the CE of different combination strategies. One study compared the CE of the combination of Talimogene Laherparepvec and Ipilimumab against Ipilimumab monotherapy. Another one, analysed the cost-effectiveness of Nivolumab combined with Ipilimumab against Ipilimumab or Nivolumab monotherapy. Lastly, one study assessed the cost-effectiveness of Ipilimumab in the second-line of treatment following Vemurafenib against Vemurafenib alone.

The QHES assessment tool revealed that the quality of six out of the nine studies included was high, and the other three despite being fair in quality, had their scores near the high-quality threshold.

KEYWORDS: Melanoma; Systematic Review; Immunotherapy; Cancer; Cost-effectiveness

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ACRONYMS

QHES – Quality of Health Economic Studies

CE – Cost-effectiveness

QoL – Quality of life

FDA – Food and Drug Administration

EMA – European Medicines Agency

VEGF – Vascular endothelial growth factor

CAR-T – Chimeric antigen receptor T-cell therapy

UV – Ultraviolet

BRAF – Proto-oncogene B-Raf

MEK – Mitogen-activated protein kinase kinase

Anti-PD1 – Anti-programmed cell death protein 1 antibody

Anti-CTLA4 – Anti-cytotoxic T-lymphocyte-associated antigen 4 antibody

NRAS – Neuroblastoma ras viral oncogene homolog

NF1 – Neurofibromatosis type 1

EBM – Evidence based medicine

RCT – Randomised clinical trial

PFS – Progression-free survival

ORR – Objective response rate

OS – Overall survival

HRQoL – Health related quality of life

PRO – Patient reported outcomes

RECIST – Response Evaluation Criteria in Solid Tumors

WHO – World Health Organization

irRECIST – Imune-related RECIST

VBM – Value-based medicine

SLR – Systematic Literature Review

HTA – Health Technology Assessment

EUnetHTA – European Network for Health Techonology Assessment

CMA – Cost-minimisation analysis

CBA – Cost-benefit analysis

CEA – Cost-effectiveness analysis

CUA – Cost-utility analysis

BIA – Budget impact analysis

COI – Cost-of-illness analysis

ICER – Incremental cost-effectiveness ratio

QALY – Quality-adjusted life years

WTP threshold – Willingness-to-pay threshold

PSA – Probabilistic senstitivity analysis

EPAR – European Public Assessment Report

ICUR – Incremental cost-utility ratio

LY – Life-years

US – United States of America

PFQALY – Progression-free quality-adjusted life years

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1 INTRODUCTION

1.1 Defining Cancer Immunotherapies

Cancer is not one disease, but the common term that is used to define a group of diseases that are defined by the uncontrolled division of cells that consequently, may lead to the disruption of the normal functions of the original cell. Cancer can arise in almost any part of the body and can be restricted in a confined area or invade other tissues via blood or lymphatic vessels. (1)

This collection of diseases is becoming more frequent in the human population and is one of the leading causes of death worldwide. It was estimated 18.1 million of new cases of cancer worldwide and 9.6 million deaths due to cancer, solely in 2018. (2)

Conventional cancer therapies, such as chemotherapeutic agents, revolutionized the treatment of cancer but are known not only for their clinical benefits but also for their many adverse effects that impair the life and productivity of the patients. Although, they have shown to be not so effective in metastasised cancers. New therapies that harness the immune system to fight cancer are in the scope of innovation in cancer therapies. This new treatment tools promise a much more targeted approach towards malignant cells and unlike conventional therapies, do not have as many adverse effects, improving the overall survival of the patient as well as their quality of life (QoL). (3)

Since the 1890s that there was the idea of fighting off cancer using the immune system, but this idea just started getting a grip during the 1950s after Macfarlane Burnet presented his theory on the “tumour immune surveillance”. (4) Since those times, we have gone a long way in defining the links between the immune system and cancer pathogenesis. It is now clear that the immune system is constantly eliminating new cancer cells until one of them escapes detection or actively suppresses the normal immune responses. These immune responses are triggered by the “neoantigens” produced by the compromised cells, and in normal circumstances the body should eliminate them, nevertheless the microenvironment produced by the tumour cells can compromise the normal immune response due to inhibitory mechanisms of immune effector cells, and in such manner eliminate the patient’s ability to further stop the development of the tumour. There is a complex balance between the immunocompetence of an individual and the immunogenicity of a tumour, that balance will dictate if there is a spontaneous elimination of the tumour; a steady-state of disease, where a few malignant cells

remain, but there is no growth of the tumour; or the escape from the immune response which will ultimately lead to the uncontrolled tumour development. (3,5,6)

The role of cancer immunotherapy is to empower the patient's immune system, either by giving it new abilities to fight cancer, such as the recognition of cancerous cells or by rebalancing the normal functions that are suppressed by malignant cells. (5)

There are four main approaches when it comes to immunotherapy for cancer, namely: The unspecific activation of the immune system, the use of targeted antibodies, cell-based immunotherapies, and therapeutic cancer vaccines. (3,7)

When it comes to the non-specific activation of the immune system, the rationale behind it is the stimulation of the patient's immune system, for instance, the inoculation of cytokines, that will promote a pro-inflammatory response that overwhelms the tumour's capacity of downregulation of the patient's immune response. (3)

The use of targeted antibodies to treat cancer was approved in the 1990s by the Food and Drug Administration (FDA) and by the European Medicines Agency (EMA), although monoclonal antibodies were already used to treat other conditions since the 80s. The mechanisms involved in the use of antibodies are varied and complex but can be summarized in three main categories, namely: the direct targeting of cancer cells, where the monoclonal antibody directly binds with surface receptors of the malignant cells and signals the immune system to destroy them; by targeting signalling pathways for the development of tumours, such as growth factors, for instance the blocking of the vascular endothelial growth factor (VEGF), which will disrupt the tumour microenvironment, by compromising the tumour neo-angiogenesis; and finally, by immunomodulation of co-stimulatory signalling of immune system, whether by blocking or engaging with the pathways responsible for the downregulation of the immune response. (3,8)

The cell-based therapies lie in the extraction of endogenous immune cells, expansion, maturation and activation ex-vivo, or additionally to those steps, genetic manipulation (eg. CAR-T technology), in order to then transfer them into the patient's body again, where they will target cancer cells with greater specificity and with a sustained effect. (3)

Finally, regarding therapeutic cancer vaccines, the rationale is to direct the host's immune system to target a specific type of tumour, by recognition of tumour-specific antigens. (3)

Over the course of the last decades cancer immunotherapies have demonstrated promising clinical outcomes and gave new hope to all people affected by these conditions. However there are some limitations associated to the use of this therapies that should be

considered. To name a few, these therapies do not work in all types of cancers, only a portion of the patients have an objective response to the treatment and the burden of adverse effects is still relevant, for instance, there are reports of 10% of the checkpoint blockade recipients experiencing serious autoimmune adverse effects that require specific management. (4,7,9)

These therapies have demonstrated in practice that they can improve the overall survival and the quality of life of cancer patients compared to conventional therapies, but innovation comes at a cost. Several factors regarding cancer immunotherapies will contribute to the growing pressure on health budgets across the globe, namely, the high cost of these therapies, the shift of these immunotherapies as the standard of care to many cancers and the use of combinations of this high-cost drugs. Thus, in a moment where the sustainability of the healthcare systems is of the utmost importance, it is crucial to consider the cost of managing and curing diseases. (10,11)

1.2 An overview of Melanoma and Immunotherapies for Advanced Melanoma

Melanoma is a type of cancer that involves malignant transformations of the melanocytes, it can develop in any part of the body that has this type of cells, such as eyes, mucous membranes, skin, and many other tissues. However, these transformations usually develop on the hair follicles in the skin. (12) This type of cancer arises from interactions between environmental exposure and genetic predisposition, being the exposure to UV radiation, the most important environmental risk factor, and the skin phenotype the most relevant risk factor regarding genetic susceptibility. (13,14)

Melanoma is the deadliest type of skin cancer and accounts for 70% of skin cancer deaths in the United States, its incidence keeps increasing worldwide, as well as its mortality did until 2016 since then mortalities have been decreasing due to prevention, early detection and new treatment strategies for advanced melanoma. (13) Unlike other types of solid tumours, this type of cancer affects mostly young and middle-aged people, the incidence of melanoma increases linearly between the 25 years of age and the 50 years of age, from that age forward the increase in incidence slows. (14) Thus, the cost-of-illness is superior when compared to other tumours that manifest later, and this is due to the fact that there are more costs attributed to the loss of productivity due to illness and loss of more years of life before the retirement age. The work of Krensel et al. estimated that melanoma costs summed up to €2.7 billion in 2012 for all the European Union and European Free Trade Association countries. (15)

Although many of the diagnoses are made at an early stage and are potentially cured, the prognosis of patients depends on the stage of the tumour at the time of the diagnose. The severity of malignant melanoma can be classified into 4 stages: Stage 1 is the less severe and corresponds to localized lesions in the epidermis; Stage 2, corresponds to localized lesions involving deeper layers of the skin; Stage 3, already involves regional lymph node metastasis; Stage 4, the most severe stage is characterized by the existence of distant metastasis. (16) Almutairi et al. stated that five-year survival rates depend on the stage of the disease at the time of the diagnosis, if the disease is diagnosed in stage 1, the five-year survival rate is at 98%, at stage 2, 90%, at stage 3, 77% and at stage 4, 10%. (17)

The management of the disease depends on the stage at the time of diagnosis. If detected at an early stage, melanoma is treated with surgery with curative intent, while ony about 10% of the patients are diagnosed with advanced or unresectable melanoma and are managed with different treatment approaches. (18)

The treatment of advanced melanoma was revolutionized since 2011, with the introduction of new treatment approaches, namely in the form targeted immunotherapies, such as pembrolizumab, nivolumab and ipilimumab, in the form of checkpoint inhibitors, such as MEK inhibitors and RAF inhibitors, and in the form of oncolytic virus, talimogene laherparepvec. (18)

Targeted immunotherapies for melanoma target immune checkpoints on T cells. Nivolumab and pembrolizumab are anti-programmed cell death protein 1 antibodies (anti-PD1), and ipilimumab is an anti-cytotoxic T-lymphocyte-associated antigen 4 antibody (anti-CTLA4). Both the CTLA-4 signalling pathway and the PD-1 axis are responsible for downregulating the activity of T cells. The treatment antibodies will block the inhibitory effects of these inhibitory pathways leading to increased antitumor immunity. (18,19) The oncolytic virus, Talimogene Laherparepvec, has a distinct mechanism of action. It infects and kills tumour cells in the area of administration, leading to local immune response. Moreover, due to the first local infection by replication of the virus and infection of distant tumour cells this drug wil lead to further subsequent local and systemic immune responses. (20)

Melanomas can be classified into four genomic subtypes, depending on their mutational driver: BRAF-mutant, NRAS-mutant, NF1-loss, and Triple wild-type. (21)

The mutational status of the advanced melanoma can likely influence the clinical responses to cancer immunotherapies since that was already proven to be true for other types of cancer. The establishment of predictive biomarkers is important to increase the proportion of recipients of the therapies achieving a durable response. Although for advanced melanoma,

this relationship is not yet clear, and the establishment of predictive biomarkers in cancer immunotherapies is proving to be challenging. (22)

A cure to metastatic melanoma does not exist. However, the introduction of new immunotherapies and targeted therapies has extended the life expectancy of the patients, and as this study is being written, more strategies are being developed to better treat those patients.

1.3 Hierarchy of Evidence and the relevance of Randomized Clinical Trials

"Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.", this was the way that David L. Sackett and his colleagues defined evidence based medicine (EBM). (23)

The concept of Evidence based medicine comprises the use of the best external evidence, the patient values and beliefs, and the individual clinical expertise of the practitioner in the decision making regarding the patient's healthcare. (24) To fully understand this concept, we should have in mind that not all sources of evidence present the same level of evidence. Therefore we shall consider all the sources of evidence and rank them accordingly, this ranking of the sources of evidence is what defines the concept of "Hierarchy of Evidence".

There are two main types of research, primary and secondary. The primary studies gather new information, such as clinical trials or surveys, while secondary studies analyse data gathered on primary studies, such as systematic reviews or even economic analysis, for instance. (25)

According to Greenhalgh et al. the source of evidence is ranked as follow (from the most robust type to the least robust type of evidence):

"(1) Systematic reviews and meta-analyses

(2) Randomised controlled trials with definitive results (confidence intervals that do not overlap the threshold clinically significant effect)

(3) Randomised controlled trials with non-definitive results (a point estimate that suggests a clinically significant effect but with confidence intervals overlapping the threshold for this effect)

(4) Cohort studies

(5) Case-control studies

(6) Cross-sectional surveys

(7) Case reports." (25)

To better understand this study, we should shed some light on the randomised clinical trials since it is from that study design that is generated the clinical data used in most cost-effectiveness studies.

Randomised clinical trials (RCTs) are the gold standard to assess the safety and efficacy of a therapeutic approach against other alternatives or against a placebo. In the first place, an RCT, like any other type of study, should be planned before being executed. First of all, it is crucial to define the study question, then define the hypothesis (superiority, equivalence, or inferiority of the intervention studied compared to the alternative) and the endpoints of the study, in other words, the variable of interest to evaluate the effect of the treatment. Afterwards, it should be defined which should be the study design, for instance, a parallel-group design, which is the format used in all of the included studies. In this methodology the study participants are divided into two groups, in which one of the groups receive an intervention and the other one receives an alternative intervention or a placebo. (26)

The study population should also be considered and selected according to inclusion and exclusion criteria, in order to achieve the comparability of both groups. Although this is one of the characteristics that allow that a causal relationship is found, it is also one of the biggest limitations in RCTs, since the study population is most of the times not representative of the real-world patients. (26)

The allocation of study subjects to each group should be done randomly, that is why the randomization is also one of the critical steps to ensure comparability and minimize confounding factors, that can ultimately lead to biased results, this randomization can be done in several ways but the most important aspect is that it should be unpredictable and should divide the study individuals in the most homogeneous way possible, to ensure that any independent variables affect the results of the study. (26)

The blinding of the study is also crucial to minimise bias. The blinding refers to the knowledge that intervening parties have about the allocation of the study population. A study is double-blinded when both patients and practitioners are unaware of the group allocation of the patient, single-blinded, when the patient is unaware of his group allocation, and finally open when all the intervening parties are aware in what group each individual was allocated. It was demonstrated that awareness of group allocation can influence the response of the intervention, thus always the maximum degree of blindness possible should be used in the randomised clinical trials in order to avoid biased results. (26,27)

Finally, the analysis of results must be adapted to the type of study being performed, and the results should be statistically tested to assess the robustness of the data gathered. (26)

1.4 Defining significative endpoints in Immuno-oncology

When it comes to immuno-oncology, some extra considerations should be taken into account when defining endpoints and assessing the test subjects' reaction to the drug. Contrary to conventional cytotoxic agents cancer immunotherapies have a limited dose-response relationship and have a long term effect even after discontinuation of the treatment, therefore traditional oncology endpoints, such as Progression-free survival (PFS) and Overall response rate (ORR), that may underestimate the long term effects of immuno-oncology drugs are not ideal for measuring the clinical efficacy of these therapies. Despite that, many accelerated approvals have been based on ORR, with the condition of these benefits being later validated by Overall Survival (OS) or PFS. (28)

The OS is defined as the time elapsed between the initiation of the treatment and the death of the patient and is the gold-standard endpoint for both conventional cytotoxic treatments and immuno-oncology agents. The PFS is defined as the period since the start of the intervention until the time where the progression of the disease or death, by any cause, happens. Finally, the ORR is defined as the proportion of patients achieving a complete or partial response to a certain intervention. (28)

Regarding the assessment of the patient’s response to immuno-oncology, there is the objective clinical assessment of the tumour evolution and health-related quality of life (HRQoL) endpoints and patient-reported outcomes (PRO). (28)

When it comes to the objective clinical assessment, the gold-standard for the assessment of tumour dynamics is the Response Evaluation Criteria in Solid Tumors (RECIST), developed based in the World Health Organization (WHO) guidelines. It provides a reliable and reproducible framework for analysis and reporting of changes in tumour dimensions. However, this assessment overlooks the patterns of response regarding cancer immunotherapies, such as pseudo-progression, for instance. Pseudo-progression is a phenomenon first described in advanced melanoma treated with ipilimumab, it is characterized by a response to treatment after progression of the disease according to the RECIST criteria, this could impact the PFS assessment given that patients can be wrongly labelled as “progressed disease” in trials, not truly reflecting the clinical benefits of the immunotherapy drug. Consequently, the irRECIST

was developed to better capture the tumour dynamics in patients treated with cancer immunotherapies. (28–30)

Regarding the subjective clinical assessment, we are addressing the patient-reported outcomes and the health-related quality of life associated to the treatment course, in oncology this is more relevant, since the survival is not the main goal of the therapy in many cases, therefore two therapies that have the same clinical efficacy can be differentiated in terms of adverse effects and overall quality of life. Hence the assessment of the PRO in cancer clinical trials is of the utmost importance as it serves as a tool to capture and quantify benefits or harm that cannot be measured by the clinical endpoints, such as symptoms or adverse effects. (28)

The HRQoL can be defined as the health status of an individual. It considers the social, physiologic and psychological state of the patient at the moment. Since it is a multidimensional evaluation, many aspects can have an impact on the HRQoL of a patient, such as symptoms, adverse effects to treatment, economic status, patient education, for instance. (31)

The quality of life of an individual can be assessed by direct methods, such as the standard gamble method or time-trade-off method, which are time-consuming and resource-intensive techniques, when compared with preference-based classifications systems, such as the EQ-5D, developed by the EuroQoL Group, which are less resource-intensive, thus more commonly used. The EQ-5D instrument is a questionnaire that encompasses five dimensions: mobility, self-care, usual activities, pain or discomfort and depression or anxiety. To this five dimensions, there are three or five levels of quantification, depending on the version of the tool used, and the consideration of all the answers by the scoring function will result in a value scale between 0 (death) and 1 (perfect health), known as utility weight. (32,33)

Furthermore, HRQoL outcomes or “utilities” are also crucial for cost-effectiveness analysis since the utility weights used in modelling of each one of the health states considered, derives from the data gathered from this assessment of the quality of life of the patients. (32) The interaction between EBM, the patient values, and the cost-utility of choosing a particular alternative is what ultimately defines Value-Based Medicine (VBM), a concept that has as goal science-based and cost-effective healthcare that considers the patients' needs, wants and beliefs. (33)

1.5 An outlook on the European Medicine Approval and HTA Landscape in Europe

After all, the technical and clinical evidence is gathered during the development of new medicines, manufacturers have three main routes to submit their request for marketing authorisation in Europe, the centralised procedure, the mutual recognition procedure, and the decentralised procedure. (34)

Although the decentralised procedure and the mutual recognition procedure are also relevant for the approval of many drugs, we are not going to describe them because only the centralised route is relevant for the medicines covered in this Systematic Literature Review (SLR). A centralised procedure is mandatory to: 1) Drugs containing new active substances with indication to treat relevant conditions, for instance, cancer; 2) Drugs derived from biotechnology processes; 3) Advanced-therapy medicines; 4) Orphan medicines; 5) Veterinary medicines for growth or yield enhancers. All the drugs in this study meet the first and second criteria. Therefore, if at the date of this study, the manufacturers were submitting their request for their marketing authorisation in Europe, they had to do it according to the centralised procedure. (34)

The centralised marketing authorisation is relevant for this type of medicine because, after the submission approval, they can be marketed in all the European member states and European Economic Area countries and therefore are in theory accessible to the patients in all the countries at the same time.

Although the submission for the Marketing Authorization is submitted to the European Medicines Agency, this institution is only responsible for the evaluation of the scientific data and the issuing of a recommendation to the European Commission, the body responsible for deciding if the product should be or not be marketed in Europe. (34)

Despite the marketing authorization being valid in all European countries there are still differences in the patient's access to newly approved medicines, since the pricing and reimbursement decisions are made on a national level, differences on the availability to new drugs are still evident, due to a number of reasons, such as, insufficient documentation from the marketing-authorization holders or differences on processes in Health Technology Assessment (HTA) bodies. (10) The HTA is a systematic method for evidence synthesis of clinical effectiveness, safety and cost-effectiveness of health technologies and is commonly used to inform decision-makers regarding reimbursement and coverage decisions. (35) Although the pricing and reimbursement decision is not a competence of the EMA, since 2010 this institution

is working closely with European Network for Health Technology Assessment (EUnetHTA), a network that encompasses governments appointed organisations, non-profit organizations and regional agencies that produce or contribute to HTA in Europe, in order to promote the generation of data for the HTA during the development of new drugs and in this way mitigate the delays in access of patients to innovative therapies. (36,37)

1.6 Defining Pharmaeconomics: Decision Analytical Modelling and Cost-effectiveness analysis

Pharmacoeconomics is regarded as a branch of health economics that encompasses the measurement, analysis, and comparison of the benefits and consequences of different pharmaceutical products and services. There are not enough health care resources to meet all the health needs, and therefore is essential to have information to prioritise the most efficient ways to meet the people's health needs in order to optimise the scarce resources available. This scarcity of resources leads to an essential concept in Health Economics, the opportunity of cost, these are the benefits that are forgone due to the choice of one alternative in spite of another. (38–40) The scarcity of resources and the social importance of health as a commodity require that decision-makers are aware of the consequences of their choices, that is where Pharmacoeconomics plays a paramount role in the development of sustainable value-based medicine.

Based on the nature of outcomes considered, there are four main types of pharmacoeconomic studies, cost-minimisation analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Nevertheless, there are other types of analysis, such as budget impact analysis (BIA) and cost-of-illness analysis (COI), these are different since they consider the economic burden of treatment alternatives and diseases, respectively, and do not necessarily consider the health benefits of treatments. (41,42)

Since only cost-effectiveness analysis and cost-utility analysis were included in this work, we will only cover these two types of pharmacoeconomic analysis in this introduction, but more information can be found in the adequate bibliography.

The cost-effectiveness analysis is only applicable when the health benefits are different amongst alternatives, and the measurement of benefits is in natural units, for instance, life-years, changes in blood pressure or blood serum glucose. One of the advantages of using natural units is that they are easy to quantify, but the disadvantage is that we cannot compare results from different studies when they do not consider the same outcome units. The results of this

type of analysis are presented as a cost-effectiveness ratio, this means that the difference between the costs and outcomes from different alternatives is divided, thus the CEA estimates not the actual cost or benefit of the alternative but rather the extra cost for each additional unit of outcome gained, the incremental cost-effectiveness ratio (ICER). The cost-utility analysis is a special type of CEA, that measures the outcomes in quality-adjusted life years (QALY) an outcome measure that will be further explained later on, but essentially considers the life-years gained with an intervention and considers the quality of life during those years, that is why it is commonly used in evaluations of chemotherapy agents. The advantage of this analysis is that it is possible to compare all health interventions, even for different diseases. Therefore it is useful to prioritise the allocation of health resources. The CUA yields the results in the form of the incremental cost-utility ratio (ICUR) that deems the additional cost per additional QALY gained. In both types of analysis, when considering if an alternative is cost-effective or not, it is usually defined a ceiling ratio, the willingness-to-pay threshold (WTP threshold). The WTP threshold is the maximum incremental cost considered reasonable to pay for each additional outcome unit provided by the intervention. The chosen alternative should be under the WTP threshold to be found cost-effective. That is better understood in Figure 1, still regarding this figure, when an alternative is located in the top left quadrant, we say it is dominated by the comparator since it more costly and less effective, and when it is located on the bottom right quadrant, we say it is dominant because it is cheaper and more effective than the comparator. (32,41,43)

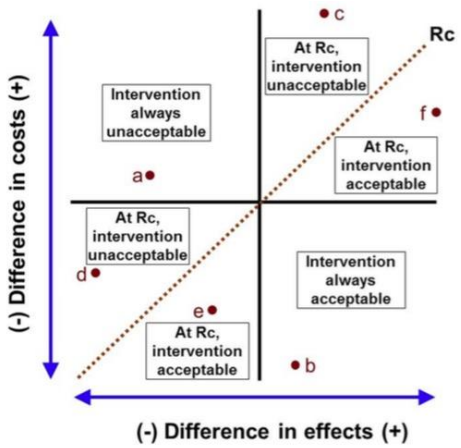


Figure 1 - Cost-effectiveness plane diagram (taken from Public Text Healthbook, David Perkins, 2017)(43)

The decision-analytical modelling is important to perform economic evaluation when there is uncertainty, for instance, in newly approved drugs. It consists of using mathematic models and probabilities to estimate the consequences of a decision or multiple decisions and the expected value in terms of outcomes in the future. There are two main approaches when it

comes to decision analytical modelling. The decision tree model is based in the probabilities of certain events happening during the course of the disease, there are numerous outcomes that can exist, such as progression of disease or death in cancer, to those outcomes an expected value of outcomes, expressed in QALYs, is estimated and moreover it is possible to calculate and identify which is the best decision. The rationale of the model is better understood in the diagrammatic representation of this process, the decision tree itself. The tree consists in branches (lines) and nodes: decision nodes, represented by squares (represent decisions that are controlled by decision-makers), chance nodes are represented by circles (that represent the possible outcomes from a previous event in the tree that is not controlled by the decision-makers, and these outcomes must be mutually exclusive, this means that they have a probability attached to each subsequent branch and the sum of the probabilities of each branch coming out of the node must be one), and finally, triangular nodes that represent the final outcome. By multiplying the expected values of potential outcomes with their probabilities, for each alternative, we get the expected value regardless of the final outcome. This model is although not suitable for diseases with time-dependent dynamic processes since it may not show all the evolution of the health status of the patient during the course of treatment, and the time between events is not usually considered. (41,43,44)

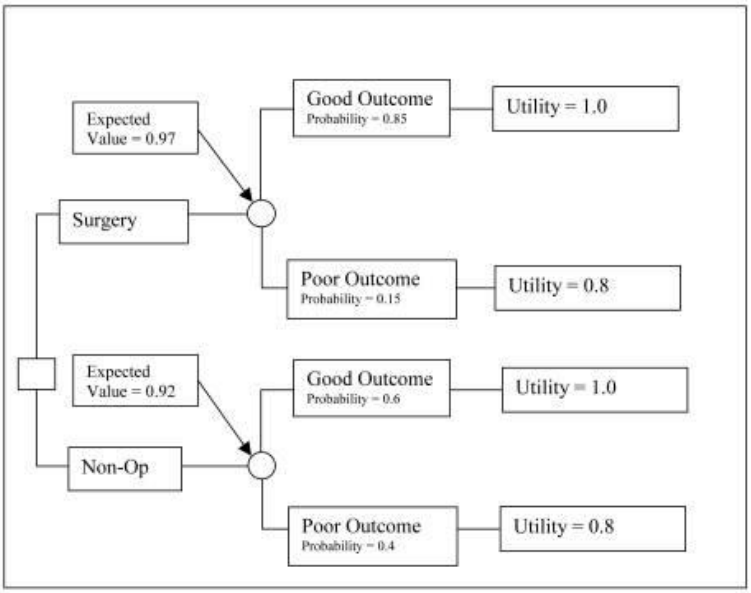
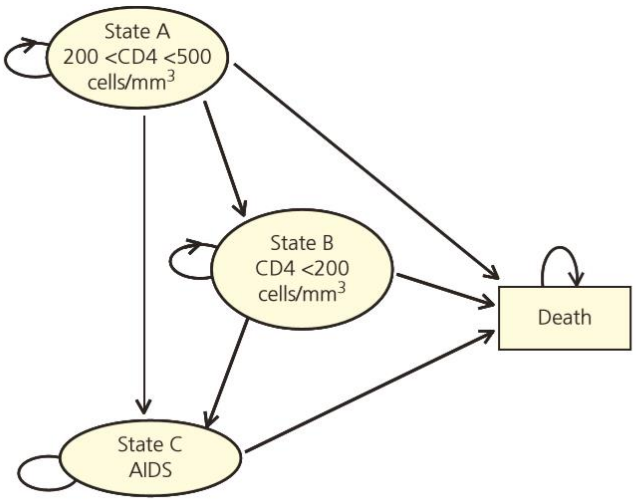


Figure 2 - Example of a basic decision-tree (taken from Decision Analysis and Cost-effectiveness Analysis, Semin Spine Surg., 2009)(44)

The Markov model has a different approach. A certain patient can be in one of the numerous health states (Markov states), each Markov state has a utility weight attached and the patients can remain in that health state or shift during each cycle (a time window considered accordingly to the pace of evolution of the disease as well as the number of cycles, this means

that fast-developing conditions have short cycles), the frequency of change between health states is related to the transition probabilities between all the health states. For instance, consider three health states commonly used in Immuno-oncology, “stable disease”, “post-progression” and “dead”. Each health state has a utility weight associated, as previously explained. At the end of each cycle, each patient can either remain in the same state or transition to another, except if he is dead, in that case, it will remain in that health state during all the next cycles, this is called an absorbing state. In the end, the time spent in each state and the cost and utilities attributed to each health state will be used to calculate expected costs and outcomes. (32,39,41)

The time horizon of the model is an important methodological consideration since it has to capture the major costs and consequences of the alternatives, although it is important to emphasise that the time horizon is usually distinct from the duration of the treatment. In the Markov model, the time horizon will dictate how many cycles the model has. (32)



Transition probabilities—monotherapy

	Transition to			
Transition from	State A	State B	State C	State D
State A	0.721	0.202	0.067	0.01
State B	0	0.581	0.407	0.012
State C	0	0	0.75	0.25
State D	0	0	0	1

Figure 3 - Example of a Markov Model with the transition probabilities for each state (taken from Methods for the Economic Evaluation of Health Care Programmes, Michael Drummond, 2015)(32)

Another key aspect of a good cost-effectiveness study is the measurement of costs. It is crucial to quantify the use of resources, the cost per unit of resource used and then valuing total resource use. However, first, it is important to define which are the most relevant types of costs related to pharmacoeconomics: Direct medical cost, are the costs directly related to the treatment itself it comprises costs such as the pharmaceutical products, costs of hospitalization,

physician fees, laboratory tests, for instance; Direct nonmedical costs, are those who are related to the treatment but have a non-medical nature, for instance, the expenses for transportation to treatment facilities, food, housing for out-of-town treatment, caregiving costs, for instance; Indirect costs, are those related to loss of productivity due to illness impairment, the absenteeism in work or early death; Finally, intangible costs are those related to the suffering, anxiety and psychological burden not only of the patients but also family and caretakers. (41)

The perspective of the analysis will define what costs should be considered and quantified since from different points of view, different costs are relevant. For instance, the nonmedical costs are usually supported only by the patient and, therefore, are not considered from a provider's perspective. There are four commonly adopted perspectives: The patient perspective, the provider perspective, the payer perspective, and the societal perspective. The patient perspective encompasses typically out-of-pocket expenses, those that are directly supported by the patient. The payer perspective includes the reimbursement costs supported by the payer (typically an employer or an insurer). The provider perspective takes into account the costs from the perspective of the hospital, so it considers the "manufacturers" costs. Lastly, the societal perspective, includes costs from all the involved parties, insurers, patients and providers, as well as indirect costs, although this is the most adequate to be taken in theory, it is usually not adopted since is time-consuming and difficult to estimate all the costs involved. (41)

Still, regarding the cost measurement, it is important to consider the timing of the costs, both past and future costs. Costs estimates from more than a year back, need to be adjusted to any inflation or deflation incurred in the previous years to be comparable to their actual values. Regarding future costs, it is primordial to understand that a certain amount of money is more valuable today than in the future since most people prefer to have money today rather than later on, therefore expected future costs and benefits must be discounted yearly by a determined rate to correspond to present values, that is called a discount rate and works in the opposite way than an interest rate would work. Discounting is an important consideration in modelling since we are doing estimations of future costs and benefits, in some cases, during the course of decades. Thus they need to be comparable to today's values. (41,43,45)

To fully understand this work, it is necessary to define the concept of quality-adjusted life years. The QALY is an outcome measure that combines the years of life with the quality of life experienced in those years. These outcomes units are calculated by multiplying the life years spent in each utility weight. Thus the advantage of this unit is to comprise results from improved mortality and morbidity in a single measure. (41)

Finally, one determinant aspect of the modelling is the sensitivity analysis of the results. As stated above, decision-analytical modelling is used for economic evaluation when there is uncertainty involved, that uncertainty arises from uncertainty in the model inputs, such as expected costs and outcomes, from model assumptions, in other words, the scientific considerations taken in account when designing the model, from the patient's heterogeneity and even from different possible outcomes from identical patients. (41,44)

A sensitivity analysis is performed by varying model parameters, such as probabilities and model inputs, to assess how those changes affect the results. This can be achieved through four different approaches: One-way analysis, which is defined by varying one key parameter at the time; Multiway analysis, in which more than one key parameter is varied at the time; Scenario analysis, in which scenarios that affect the key parameters are constructed, they are especially useful to test scenarios that researchers think that are likely to happen or assess the impact of structural assumptions of the model; Lastly, the probabilistic sensitivity analysis (PSA), in which is defined a possible range for the parameters, that are drawn randomly a defined number of times to generate an empirical distribution of the costs and outcomes. (32)

Thus, sensitivity analysis is important to determine the robustness of the analysis results. To illustrate, if small changes influence the results in the parameters, more caution is needed when considering the study results.

1.7 Aim of the study

Considering the added value of using cancer immunotherapies to treat advanced melanoma, the necessity of establishing the most cost-effective ways to do so and at the same time assuring the sustainability of health care systems, this study was designed with the purpose of review, systematize and assess the quality of cost-effectiveness evidence of cancer immunotherapy drugs for advanced melanoma by gathering and presenting all the relevant information that can help decision-makers decide about which are the most cost-effective ways of treating advanced melanoma and simultaneously guide further research on the topic.

2 MATERIALS AND METHODS

2.1 Drug Master List

A comprehensive search was performed in the EMA's European Public Assessment Report (EPAR) database for targeted immunotherapies with at least one cancer indication and an active marketing authorization, till the 6th of March 2019. The list of included medicines, as well as their indications to that date and other relevant information, is present in the attachments.

2.2 Database Search

A search on Pubmed was conducted for studies on cost-effectiveness and cost-utility of the drugs included in the Drug Master List, the time horizon contemplated on the search query was from the 1st of January 2013 till the 6th of March 2019. The search profile used in Pubmed was as follows "(cost-effective*[Title/Abstract] OR "costs and cost analysis"[MeSH] OR cost-utility[Title/Abstract]) AND cancer AND (brentuximab vedotin OR ofatumumab OR bevacizumab OR avelumab OR inotuzomab ozogamicin OR blinatumomab OR ramucirumab OR daratumumab OR elotuzumab OR cetuximab OR obinutuzumab OR trastuzumab OR durvalumab OR talimogene laherparepvec OR trastuzumab emtansine OR pembrolizumab OR tisagenlecleucel OR olaratumab OR rituximab OR gemtuzumab ozogamicin OR nivolumab OR pertuzumab OR necitumumab OR dinutuximab beta OR atezolizumab OR ibritumomab tiuxetan OR panitumumab OR ipilimumab OR axicabtagene ciloleucel)".

2.3 Selection of Included Studies

A Title/Abstract screen was used to select the included studies. Two independent reviewers conducted it in order to eliminate bias from subjective assessment and partial judgement. From the 480 studies, the first screen resulted in a total of 165 articles between the two independent reviewers, including the systematic reviews and excluded articles. From those 165 articles, a total of 17 were relevant systematic reviews, which are identified in the attachments. Eight studies were excluded after discussion with a third independent reviewer,

and four more studies were not included in the final tables due to lack of information in the full-text, leading to a total of 136 studies included. The inclusion criteria for considered were: English publications only; Study in question had cost-effectiveness and/or cost-utility and/or cost-benefit evaluations; At least one of the drugs in the Drug Master List was included; and finally, the economic evaluation in question must be for a cancer indication.

Regarding the exclusion criteria, Systematic Literature Reviews were not included in this study but are available in the attachments of this work all the systematic reviews that met all the inclusion criteria of this review. The results were then treated and separated accordingly to the type of cancer, resulting in the following categories (number of studies): Bladder Cancer (1); Brain Cancer (1); Breast Cancer (20); Cervical Cancer (3); Colorectal Cancer (24); Endometrial Cancer (1); Esophageal Cancer (1); Gastric Cancer (3); Head and Neck Cancer (6); Leukemia (12); Lymphoma (16); Melanoma (9); Merkel Cell Carcinoma (1); Multiple Myeloma (3); Non Small Cell Lung Cancer (19); Ovarian Cancer (9); Pleural Mesothelioma (1); and finally, Renal Cell Carcinoma (6) . For this work, only studies on advanced melanoma were included. Nevertheless, all the studies are presented in the attachments section of this work by type of cancer but are not going to be analysed or discussed because that is out of the scope of this study.

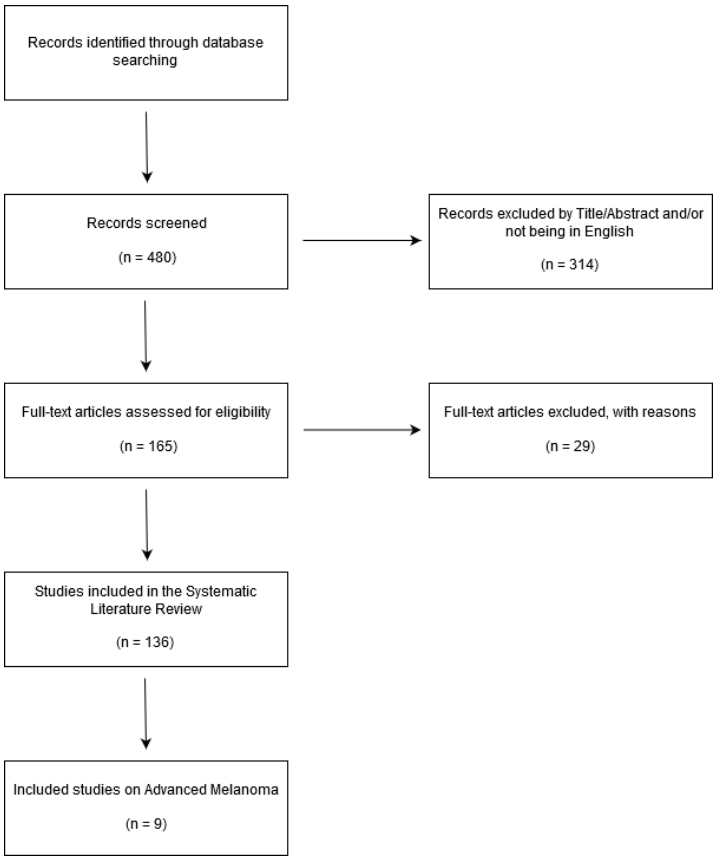


Figure 4 - Flow diagram of the selection of the studies

2.4 Data Extraction

The data considered pertinent for the analysis of the studies was decided after discussion by three independent reviewers, it was decided that relevant data consisted in: Title of the study; Name of the first author; The year of the publication; The Country of the study; The target population; The main intervention or interventions; The comparators used; The perspective of the study; The time horizon considered; The sources of the parameters used in the models (Parameter Sources); The Willingness-to-pay (WTP) threshold; The costs (C) and outcomes (O) discount rates; The modelling approach used (Approach); The clinical outcomes generated by the model or considered if no modelling approach was used (Effect); The cost parameters generated by the model or considered if no modelling approach was used (Cost); The incremental cost-effectiveness ratio (ICER) or the incremental cost-utility ratio (ICUR); and finally the main conclusion taken from the study.

The majority of the data presented in the results was extracted from the abstract. When at least one of the items was not specified in the abstract a full-text data extraction was conducted. Furthermore, some items were simplified to present the data in a more systematic way. Namely, regarding the perspective of the studies, when was implied the perspective even if it was not stated it would be categorized in one of four categories (Payer, Societal, Patient or Other), regarding the modelling approach, it was considered the stated method as long as it was a Partitioned Survival Model, a Markov Model, a Semi-Markov Model, a Decision Analytical Model or a Decision Tree Model, any other approach was labeled as Other, and finally concerning the time horizon, any study that had a perspective longer than 30 years was considered a lifetime horizon.

2.5 Appraisal of the quality of the studies included with the Quality of Health Economic Studies (QHES) instrument

The QHES instrument is a validated method that can be used to evaluate the relative quality of cost-effectiveness and cost-utility studies. It consists of 16 questions addressing the appropriateness of the methodologies used, the clarity and reliability of the results, as well as the quality of the reporting of those results. (46)

	Questions	Points	Yes	No
1)	Was the study objective presented in a clear, specific, and measurable manner?	7		
2)	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4		
3)	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial -best, expert opinion -worst)?	8		
4)	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1		
5)	Was uncertainty handled by (1) statistical analysis to address random events, (2) sensitivity analysis to cover a range of assumptions?	9		
6)	Was incremental analysis performed between alternatives forresources and costs?	6		
7)	Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5		
8)	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7		
9)	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8		
10)	Were the primary outcome measure(s) for the economic evaluation clearly stated and did they include the major short-term, long-term, and negative outcomes?	6		
11)	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7		
12)	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8		
13)	Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7		
14)	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6		
15)	Were the conclusions/recommendations of the study justified and based on the study results?	8		
16)	Was there a statement disclosing the source of funding for the study?	3		
	Total Points	100		

Figure 5 - The Quality of Health Economic Studies (QHES) instrument (adapted from A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer., European Journal of Cancer, 2014) (47)

This tool is a checklist, and therefore for each checked item, there is a weighted score associated. After summing the scores obtained in every item of the checklist, the highest a study can score is 100 points, and the lowest is 0 points. According to Lange et al., the studies can be ranked in four quality categories: extremely poor quality (0-24); poor quality (25-49); fair quality (50-74); and high quality (75-100). (47)

In this QHES assessment, a slight adaptation on question 8 was made. It was considered that as long as the benefits and costs were discounted between 3% and 5%, there was no need to justify the choice of the discount rates.

3 RESULTS

3.1 Pembrolizumab vs Ipilimumab

Table 1 - Summary of the included publications

Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal.; Miguel LS.; 2017; Portugal	**Target Population:** Patients with advanced melanoma not previously treated with ipilimumab **Intervention:** Pembrolizumab **Comparators:** Ipilimumab	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Expert panel, clinical trials, published studies and databse **WTP threshold:** €50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** An increase of 0.98 QALY per patient, from 2.33 with ipilimumab to 3.31 with pembrolizumab. **Cost:** An incremental total cost of €46,233 per patient with pembrolizumab compared with ipilumumab	**ICER/ICUR:** €47,221/QALY and €42,956/LY **Main conclusion:** Considering the usually accepted thresholds in oncology, pembrolizumab is a cost-effective alternative for treating patients with advanced melanoma in Portugal.
Cost-Effectiveness of Pembrolizumab Versus Ipilimumab in Ipilimumab-Naïve Patients with Advanced Melanoma in the United States.; Wang J.; 2017; United States	**Target Population:** Patients with unresectable or meta-static melanoma **Intervention:** Pembrolizumab **Comparators:** Ipilimumab	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Database, published studies, clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** In the base case, pembrolizumab was projected to increase the life expectancy of U.S. patients with advanced melanoma by 1.14 years, corresponding to a gain of 0.79 discounted QALYs over ipilimumab **Cost:** The model also projected an average increase of $63,680 in discounted perpatient costs of treatment with pembrolizumab versus ipilimumab	**ICER/ICUR:** $81,091/QALY and $68,712/LY **Main conclusion:** Compared with ipilimumab, pembrolizumab had higher expected QALYs and was cost-effective for the treatment of patients with unresectable or metastatic melanoma from a U.S. integrated health system perspective.

Two studies evaluated the cost-effectiveness of pembrolizumab against ipilimumab.

Miguel et al. (48) assessed the cost-effectiveness of pembrolizumab against ipilimumab, in the first or second line of treatment, in patients with advanced melanoma not previously treated with ipilimumab. His study adopted the Portuguese National Health Service perspective, and with a base case scenario ICER of €47,221 per QALY gained, pembrolizumab was considered a cost-effective medicine for the treatment of advanced melanoma in the Portuguese setting. Furthermore, the robustness of these results was confirmed by the probabilistic sensitivity analysis since the ICER was below the €50,000 WTP threshold in 75% of the cases.

From a U.S. integrated health system perspective, Wang et al. (49), considered that Pembrolizumab was a cost-effectiveness alternative compared with ipilimumab for the treatment of advanced melanoma in patients not previously treated with ipilimumab in the United States. The base case scenario ICER was $81,091 per QALY gained and $68,712 per LY gained, and in the PSA, pembrolizumab was still cost-effective in 83% of the cases.

3.2 **Nivolumab vs Ipilimumab**

Table 17 - Summary of the included publications (cont.)

Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
The cost-effectiveness of nivolumab monotherapy for the treatment of advanced melanoma patients in England; Meng Y.; 2018; England	**Target Population:** Advanced melanoma patients **Intervention:** Nivolumab **Comparators:** BRAF+ patients: ipilimumab and dacarbazine BRAF- patients: ipilimumab, dabrafenib, and vemurafenib	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** £50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Markov Model	**Effect:** For BRAF+ patients, nivolumab is estimated to be most effective (4.27 QALYs) compared to ipilimumab (2.44 QALYs), dabrafenib (1.69 QALYs) and vemurafenib (2.37 QALYs). For BRAF– patients, nivolumab is most effective (4.31 QALYs) compared to dacarbazine (1.23 QALYs) and ipilimumab (2.64 QALYs). **Cost:** For BRAF +ve patients, nivolumab is estimated to be the most costly (£88,228) compared to ipilimumab (£56,621), dabrafenib (£71,511) and vemurafenib (£74,001).For BRAF –ve patients, nivolumab is the most costly (£97,898) compared to dacarbazine (£25,228) and ipilimumab (£57,158).	**ICER/ICUR:** BRAF+ = £17,362/QALY and BRAF- = £24,483/QALY **Main conclusion:** Nivolumab is a cost-effective treatment for advanced melanoma patients in England
A Cost-Effectiveness Analysis of Nivolumab Compared with Ipilimumab for the Treatment of BRAF Wild-Type Advanced Melanoma in Australia.; Bohensky MA.; 2016; Australia	**Target Population:** Previously untreated patients with BRAF-advanced melanoma **Intervention:** Nivolumab **Comparators:** Ipilimumab	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, Published studies and clinical trials **WTP threshold:** US $35,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** Compared with ipilimumab, nivolumab therapy over 10 years was estimated to yield 1.58 life-years and 1.30 quality-adjusted life-years per person **Cost:** Compared with ipilimumab, nivolumab therapy over 10 years was estimated to have a (discounted) net cost of US $39,039 per person.	**ICER/ICUR:** $25,101 per year of life saved and $30,475/QALY **Main conclusion:** Nivolumab is a cost-effective means of preventing downstream mortality and morbidity in patients with AM compared with ipilimumab in the Australian setting.

The work of Meng et al. (50) assessed the cost-effectiveness of nivolumab in BRAF negative-mutation and BRAF positive-mutation advanced melanoma patients. In the BRAF negative-mutation subgroup, nivolumab against dacarbazine had an ICER of £24,483 per QALY gained while ipilimumab against the same comparator had an ICER of 22,589 per QALY gained. In the BRAF positive-mutation subgroup, nivolumab against ipilimumab yielded an ICER of £17,362 per QALY. Nivolumab proved to be cost-effective alternative in the English setting in both BRAF positive and negative mutation subgroups.

The cost-effectiveness of nivolumab against ipilimumab in the treatment of BRAF negative-mutation advanced melanoma patients from the Australian health system was conducted by Bohensky et al. (51). In the base case scenario, nivolumab yielded an ICER of US$25,101 per LY gained and US$30,475 per QALY gained. In the Monte-Carlo simulation, it was shown that nivolumab was cost-effective 59% of the cases considering a WTP threshold of US$35,000.

3.3 **Ipilimumab vs Vemurafenib**

Table 33 - Summary of the included publications (cont.)

Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma.; Curl P.; 2014; United States	**Target Population:** Treatment-naïve patients with BRAF-mutated metastatic or unresectable melanoma **Intervention:** Ipilimumab + Vemurafenib ; Vemurafenib **Comparators:** Dacarbazine; Vemurafenib	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical	**Effect:** There was an incremental 0.62 QALYs with Ipilimumab + Vemurafenib strategy compared with Dacarbazine alone **Cost:** There was an incremental cost of $97,864 with Ipilimumab + Vemurafenib strategy compared with Dacarbazine alone	**ICER/ICUR:** $158,139/QALY **Main conclusion:** The cost per QALY gained for treatment of BRAF+ metastatic melanoma with vemurafenib alone or in combination exceeds widely-cited thresholds for cost-effectiveness. These strategies may become cost-effective with lower drug prices or confirmation of a durable response without continued treatment.

From a societal perspective, Curl et al. (52) assessed the cost-effectiveness of ipilimumab as second-line treatment following the use of vemurafenib against vemurafenib alone in patients not previously treated with BRAF mutated advanced melanoma. With an ICER of $158,139 per QALY gained, this treatment strategy was not considered cost-effective, being above the WTP threshold of $100,000 per QALY gained considered in the study.

3.4 **Sequential Treatment Approaches**

Table 49 - Summary of the included publications (cont.)

Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
Sequential treatment approaches in the management of BRAF wild-type advanced melanoma: a cost-effectiveness analysis.; Tarhini A.; 2018; United States	**Target Population:** Patients with BRAF wild-type melanoma. **Intervention:** 1) 1L Anti-CTLA-4; 2L Anti-PD-1; 3L Chemo/BSC and 2) 1L Anti-PD-1; 2L Anti-CTLA-4; 3L Chemo/BSC and 3) 1L Anti-PD-1 + anti-CTLA-4; 2L Chemo; 3L Chemo/BSC and 4) 1L Anti-PD-1 + anti-CTLA-4; 2L Anti-PD-1; 3L Chemo/BSC **Comparators:** Against each other	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, clinical trials, database and expert opinion **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** -	**Effect:** 3.64 QALYs for sequence 1; 4.91 QALYs for sequence 2; 5.90 QALYs for sequence 3 and 5.84 QALYs for sequence 4 **Cost:** $343,542 for sequence 1; $319,082 for sequence 2; $349,707 for sequence 3 and $450,544 for sequence 4	**ICER/ICUR:** 1) Dominant (vs 2) and $2,739/QALY (vs 3) and $48,802/QALY (vs 4) ; 2) Dominated (vs 1) and $30,955/QALY (vs 3) and $141,213/QALY (vs 4) ; 3) = $2,739/QALY (vs 1) and $30,955/QALY (vs 2) and Dominated (vs 4) ; 4) = $48,802/QALY (vs 1) and $141,213/QALY (vs 2) and Dominant (vs 3) **Main conclusion:** Anti-PD-1 + anti-CTLA-4 initiating sequences for BRAF wild-type melanoma are cost-effective versus anti-PD-1.
Cost-Effectiveness of Immune Checkpoint Inhibition in BRAF Wild-Type Advanced Melanoma.; Kohn CG; 2017; United States	**Target Population:** Patients with BRAF wild-type metastatic melanoma **Intervention:** Nivolumab, Ipilimumab ; Nivolumab + Ipilimumab , Pembrolizumab every 2 weeks; Pembrolizumab every 3 weeks; Dacarbazine **Comparators:** Against each other	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Compared with the treatment strategy with PEM every 3 weeks, first-line NIVO was associated with incremental of 0.16 QALYs, whereas first-line NIVO + IPI was the least cost-effective strategy and was associated with benefits of 0.18 QALYs. **Cost:** Compared with the treatment strategy with PEM every 3 weeks, first-line NIVO was associated with incremental costs of $44,593, whereas first-line NIVO + IPI was the least cost-effective strategy and was associated with an additional $78,809 in costs.	**ICER/ICUR:** PEM every 3 weeks followed by second-line IPI was both more effective and less costly than dacarbazine followed by IPI then NIVO, or IPI followed by NIVO. Compared with the first-line dacarbazine treatment strategy, NIVO followed by IPI produced an ICER of $90,871/QALY, and first-line NIVO + IPI followed by carboplatin plus paclitaxel chemotherapy produced an ICER of $198,867/QALY. **Main conclusion:** For patients with treatment-naive BRAF wild-type advanced melanoma, first-line PEM every 3 weeks followed by second-line IPI or first-line NIVO followed by second-line IPI are the most cost-effective, immune-based treatment strategies for metastatic melanoma.

Two studies evaluated the cost-effectiveness of different sequential approaches in the treatment of advanced melanoma. From a U.S. third-party payer perspective, Tarhini et al. (53) assessed the cost-effectiveness of different sequential approaches from the first line till the third line of therapies, considered the use of the following drugs: an anti-CTLA-4 agent (ipilimumab), an anti-PD-1 agent (nivolumab and pembrolizumab in equal share), a combination of an anti-PD-1 and an anti-CTLA-4 agent and chemotherapy (a mix of dacarbazine, temozolomide, paclitaxel and carboplatin and paclitaxel) or best supportive care, in a pairwise comparison. The most cost-effective sequence was the use of combination therapy as first-line therapy followed by chemotherapy in the second line and by chemotherapy or best supportive care in the third line of treatment.

Also from a US payer perspective, Kohn et al. (54) evaluated the cost-effectiveness of different sequential approaches in multiple combinations, varying the number of lines of treatment per approach. Nivolumab, ipilimumab, pembrolizumab every 2 or 3 weeks, and a combination of nivolumab and ipilimumab were considered as agents in this study. It was always assumed response to the first line of treatment in every sequence of treatments. The most cost-effective sequence of treatments was the first line of treatment with pembrolizumab every 3 weeks, followed by ipilimumab as the second-line therapy.

3.5 **Combination therapies**

Table 65 - Summary of the included publications (cont.)

Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
Economic Evaluation of Talimogene Laherparepvec Plus Ipilimumab Combination Therapy vs Ipilimumab Monotherapy in Patients With Advanced Unresectable Melanoma.; Almutairi AR.; 2019; United States	**Target Population:** Patients with advanced unresectable melanoma **Intervention:** Talimogene laherparepvec + Ipilimumab **Comparators:** Ipilimumab	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, clinical trials and database **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The progression free life-years were estimated to be 1.15 vs 0.98 for ipilimumab alone, and the progression-free QALYs were estimated to be 0.95 vs 0.79 **Cost:** The cost of talimogene laherparepvec plus ipilimumab ($494 983) exceeded the cost of ipilimumab monotherapy ($132 950) by $362 033.	**ICER/ICUR:** The ICER was $2 129 606 per PFS life-years, and the ICUR was $2 262 706 per PFS quality-adjusted life-year gained. **Main conclusion:** The cost to gain 1 additional progression-free quality-adjusted life-year, 1 additional progression-free life-year, or to have 1 additional patient attain objective response is about $1.6 million. This amount may be beyond what payers typically are willing to pay. Combination therapy of talimogene laherparepvec plus ipilimumab does not offer an economically beneficial treatment option relative to ipilimumab monotherapy at the population level. This should not preclude treatment for individual patients for whom this regimen may be indicated.
Cost-Effectiveness of Nivolumab-Ipilimumab Combination Therapy Compared with Monotherapy for First-Line Treatment of Metastatic Melanoma in the United States.; Oh A.; 2017; United States	**Target Population:** First-line therapy in metastatic melanoma **Intervention:** Nivolumab + Ipilimumab **Comparators:** Nivolumab ; Ipilimumab	**Perspective:** Societal **Time Horizon:** 14,5 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/PFQALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Combination therapy provided an additional 0.69 PFQALYs with an incremental cost of $14,589 compared to ipilimumab and an additional 0.13 PFQALYs with an incremental cost of $59,032 compared to nivolumab. **Cost:** In the base case analysis, which represents our best available estimates, nivolumab monotherapy had the lowest overall cost at $169,320, followed by ipilimumab monotherapy at $213,763, and combination therapy, which was the most expensive at $228,352	**ICER/ICUR:** $454,092/PFQALY (vs nivolumab) and $21,143/PFQALY (vs Ipilimumab) **Main conclusion:** Nivolumab-ipilimumab combination therapy was not cost-effective compared with nivolumab monotherapy, which was the most cost-effective option. Professionals in managed care settings should consider the pharmacoeconomic implications of these new immunotherapies as they make value-based formulary decisions, and future cost-effectiveness studies are completed.

Two studies assessed the cost-effectiveness of different combination therapies for the treatment of advanced melanoma.

The most recent one, a study by Almutairi et al. (17), is a cost-effectiveness evaluation of talimogene laherparepvec combined with ipilimumab against ipilimumab alone for patients with advanced melanoma. From a US payer perspective, the base case scenario resulted in an ICER of $2,129,606 per progression-free life-year gained and in an ICUR of $2,262,706 per progression-free QALY gained. In the sub-analyses performed, the ICERs were $1,069,044 per additional patient with BRAF wild-type achieving an objective response and $17,104,700 per additional patient with BRAF mutant status achieving an objective response. This combination of talimogene laherparepvec and ipilimumab was considered not cost-effective compared with ipilimumab alone in the United States setting.

Finally, the work of Oh et al. (55) assessed the cost-effectiveness of nivolumab and ipilimumab combination against nivolumab alone and ipilimumab alone in patients with advanced melanoma, from a U.S. societal perspective. With a WTP threshold of $100,000 per PFQALY gained, the combination therapy was considered cost-effective against ipilimumab but not cost-effective against nivolumab, the ICERs calculated in the base case scenario were $21,143 per PFQALY gained and $454,092 per PFQALY gained, respectively.

3.6 **Assessment of the Quality of the Included Studies**

Table 95 - Results of the Quality of Health Econonic Studies (QHES) assessment

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total Points
Almutairi et al. (2019)	✓	X	✓	✓	✓	X	X	✓	✓	X	✓	✓	✓	X	✓	✓	73
Tarhini et al. (2018)	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	88
Meng et al. (2018)	✓	X	X	✓	✓	✓	✓	X	X	✓	✓	✓	✓	X	✓	✓	67
Miguel et al. (2017)	✓	X	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	82
Oh et al. (2017)	✓	X	✓	✓	✓	✓	✓	✓	✓	X	X	✓	✓	X	✓	✓	77
Kohn et al. (2017)	✓	X	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	X	✓	X	81
Wang et al. (2017)	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	✓	86
Bohensky et al. (2016)	✓	X	X	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X	✓	X	79
Curl et al. (2014)	✓	X	✓	✓	X	✓	✓	✓	X	✓	✓	✓	✓	X	✓	✓	73
Yes frequency	9	2	5	9	8	6	8	8	7	7	8	0	9	0	9	7	78,4 (Average)

The results from the evaluation performed with the QHES tool are present on Table 4, we can state that the average quality of the studies included is at a high-quality level with a mean of 78,4 points per study (standard deviation: 6,7), furthermore only 3 studies did not achieve a high-quality score (17,50,52), but they were still close to the high-quality score threshold.

The objectives of the studies were clearly described in all nine studies. (Question 1). Despite the perspective of the analysis was stated in all of the studies except in the work of Meng et al. (50), although an NHS perspective was clearly implied, only Tarhini et al. (53) and Wang et al. (49) explicitly stated the reasons for the selection of the perspective. (Question 2).

Almost half of the studies included (48–51) may not have used the best available source for the estimation of model variables. (Question 3).

In every study, when estimates came from a subgroup analysis, the groups were pre-specified at the beginning of the study. (Question 4).

All the included studies have handled uncertainty by extensive statistical and sensitivity analyses, except for Curl et al. (52) that despite performing sensitivity analysis, did not address the possibility of random events in a thorough manner. (Question 5).

Although in all the studies an incremental analysis was performed since this was a criterion of inclusion for this study, three studies (17,53,54) did not explicitly state the incremental cost and resource use between alternatives. (Question 6).

Almutairi et al. (17) did not specify any of the methodology used for data abstraction of the variables used in the model (Question 7). In the study conducted by Meng et al. (50), the discounting of costs and benefits was not stated. Moreover, it was not even possible to understand if the discounting was done. (Question 8). Two studies had issues regarding the methodology used in resource utilisation estimation. The study conducted by Almutairi et al.

(17) did not specify the methodology used in the measurement of resource utilisation neither the unit cost attributed to the different parameters. The evaluation performed by Curl et al. (52) did not specify the methodology used for estimating the resource utilisation. (Question 9). The works of Almutairi et al. (17) and Oh et al. (55) did not address the major long-term effects of the alternatives since the modelling was done until progression or death, and therefore the progressive disease state was not considered in their analyses. (Question 10). Regarding the health outcomes measures used in the studies, Oh et al. (55) used PFQALY to quantify the results but did not give enough justification for the choice of this measurement unit. (Question 11). All the included studies presented the economic model, study methods and inputs transparently and clearly (Question 12). The choice of the economic model, as well as the main assumption and limitations of the study, were stated and justified in all the analyses (Question 13). However, any of the authors explicitly discuss the direction and magnitude of potential biases. (Question 14). In every study, the author's conclusion was based and justified on the study results. (Question 15). Two studies (51,54) did not have a statement disclosing the source of funding for the study. (Question 16)

4 DISCUSSION

This study, although focused on immunotherapies for advanced malignant melanoma, presents useful research data that can serve as a base for further systematic literature reviews on immuno-oncology for other types of cancer. This fact is due to the broad search profile used. However, the broadness of the search profile was chosen with two intentions in mind. First, to avoid missing studies that could fit in the inclusion and exclusion criteria. Secondly, to provide an overview of the cost-effectiveness analysis that were produced regarding cancer immunotherapy agents regardless of the type of cancer they are intended to treat.

To our knowledge, two other studies reviewed the cost-effectiveness of immunotherapies for advanced melanoma. (56,57) The work of Jonhston et al. assessed the cost-effectiveness of ipilimumab alone against the best supportive care, considering the higher acceptable costs in the context of oncology and the clinical benefits yielded compared to available therapies at the time, it was considered a good value for money option. Regarding the work of Pike et al., discrepancies were found between his study results and the results of the present study. Those discrepancies can be due to the fact that in that study, dacarbazine was used as the active comparator against all other alternatives. When in that study, the combination of nivolumab and ipilimumab, nivolumab alone, and pembrolizumab alone, were compared against ipilimumab, all the ICERs, except for the combination approach, were below the contemplated WTP threshold.

In the study performed by Almutairi et al., talimogene laherparepvec combined with ipilimumab was not cost-effective in any scenario since this combination had only a slight improvement on PFS and had a gigantic incremental cost when compared against ipilimumab alone, however the percentage of patients achieving an objective response was significantly higher (38.8% vs 18%). The modelling was based on data from phase II clinical studies used for the accelerated approval of the medicine, and more robust research should be done regarding the full potential benefits of this innovative strategy.

More studies on cost-effectiveness is a transversal need in immuno-oncology for advanced melanoma since all the included studies that used OS as a clinical endpoint, extrapolated the long term OS from data from previously published clinical trials. As it is known the real-world efficacy of a medicine (or effectiveness) is far different from the efficacy from an RCT, thus the conclusions of these studies should be corroborated and compared with studies

based in real-world evidence, in order to cover, for instance, unforeseen benefits in OS due to limited follow-up time in RCT, unexpected adverse events and real-world costs.

Regarding the results of all included studies that compared both anti-PD1 agents alone, nivolumab and pembrolizumab, against ipilimumab alone (anti-CTLA4), considered those anti-PD1 antibodies cost-effective alternatives. It is also important to refer that the work of Meng et al. used a subgroup analysis based on the BRAF mutation status of the patients, that analysis revealed that nivolumab was cost-effective against all the active comparators used regardless of the BRAF mutation status. Both nivolumab and pembrolizumab, appear to be good candidates as first-line treatment of advanced melanoma, as they proved to be cost-effective in different settings, furthermore according to Kohn et al. it seems that using anti-PD1 agents as first-line yields better results when compared with using them in later lines of treatment and they seem to be effective regardless of the PD1 status of the patient. (19) Also, there was not any study that compared the cost-effectiveness of pembrolizumab against nivolumab, and both alternatives could not be compared head-to-head.

The results from the work of Meng et al. deemed the combination therapy of nivolumab with ipilimumab cost-effective against ipilimumab alone, however the combination of both agents was dominated when compared to nivolumab alone in the first-line of treatment, however the combination treatment is not cost-effective with the $100,000/PFQALY against both comparators, if the patient has PD-L1 status negative. One important factor related to combination therapies is that despite increasing the response to treatment and survival, they present more adverse effects on patients, this translates into more patients discontinuing the treatment and higher costs of managing side effect, this factor should be weighted when considering the use of combination therapies.

The works of Kohn et al. and Tarhini et al. on sequential treatment regimens for BRAF mutation-negative patients are similar but have significant contradictions when it comes to conclusions. Kohn et al. states that the most cost-effective sequential approach is first-line therapy with an anti-PD-L1 agent followed by ipilimumab as second-line treatment, while Tarhini et al. claims the most cost-effective approaches are either the combination of an anti-PD1 agent and an anti-CTLA4 agent followed by conventional chemotherapy in the subsequent lines of treatment or a combination of anti-PD1 and anti-CTLA4 followed by an anti-PD1 as second-line treatment followed by conventional chemotherapy as third-line of treatment. The contradiction in these two studies is most likely related to different model assumptions and different estimations, both in costs and benefits. This contradiction is a clear example that

reinforces the importance of corroborating the cost-effectiveness data gathered in studies with real-world evidence.

Furthermore, the interpretation of the results of the quality assessment of the included studies should be made with caution due to the subjective nature of this tool, even more in this case where the quality assessment was performed by a single reviewer. Despite that, the included studies have revealed a similar approach and high quality in the included pharmacoeconomic studies performed in recent years.

It is clear that cancer immunotherapies changed the paradigm in terms of treatment in advanced melanoma, they significantly improved survival and the quality of life of patients treated with these medicines, but much more research is needed in this recent field, whether in optimal dosing or predictive biomarkers to optimize response. However, it was possible to assess in this study that targeted immunotherapies, especially anti-PD1 agents are a cost-effective approach in managing advanced melanoma in developed countries. However, it is crucial to have in mind that cost-effectiveness does not necessarily translate into affordability. Cost-effectiveness analysis merely has into account the cost efficiency of one alternative compared against another one and does not consider the prevalence and incidence of a disease. Thus it does not incorporate the financial burden of managing a disease with a particular alternative as a standard of care. With the high costs that these immunotherapies pose, it is crucial to establish criteria in order to avoid waste. In other words, maximise objective response rates and clinical benefits and in that way, assure the healthcare systems sustainability. (10)

Limitations of this Study

This study has some limitations. Namely, it may be threatened by publication bias. Although a broad search profile was used to search in the literature having this limitation in mind, only Pubmed was searched, many other databases should have been used to complement this database search, such as Cochrane Library, MEDLINE, EMBASE, for instance. However, access to those institutional databases was not possible. Therefore, if further work is based on this study, more databases need to be used.

Another limitation regarding this study that was already referred above is the quality assessment of the included studies, due to the subjective nature of the questionnaire itself. Moreover, blinding of the studies should have been done to avoid potential judgment bias, but this was not possible since the reviewer was the main author.

5 CONCLUSION

This study revealed that anti-PD1 agents, such as pembrolizumab and nivolumab, are cost-effective ways of treating advanced melanoma. However, the cost-effectiveness of combination therapies between these agents and an anti-CTLA 4 drug, such as ipilimumab is still controversial since the adverse effects and the high cost of this approach may offset its benefits. The most cost-effective sequencial approach is not yet defined since ambiguous results were yield. The combination of Talimogene Laherparepvec was not cost-effective but revealed some exciting results that, in our opinion, should be further explored.

We conclude that further investigation is prioritary in the way of establishing optimal dosing regimens and defining predictive biomarkers that can help to streamline the management of advanced melanoma with cancer immunotherapies but also to define the most cost-effective sequencial approach to treat patients affected by this type of cancer, in order to ensure the sustainable use of these immunotherapies for the future.

6 REFERENCES

1. What Is Cancer? - National Cancer Institute [Internet]. [cited 2019 Nov 6]. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018 Nov [cited 2019 Nov 6];68(6):394–424. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30207593

3. Helmy KY, Patel SA, Nahas GR, Rameshwar P. Cancer immunotherapy: accomplishments to date and future promise. Ther Deliv [Internet]. 2013 Oct [cited 2019 Nov 6];4(10):1307–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24116914

4. Trapani JA, Darcy PK. Immunotherapy of cancer. Aust Fam Physician [Internet]. 2017 [cited 2019 Nov 6];46(4):194–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28376571

5. Finn OJ. Immuno-oncology: understanding the function and dysfunction of the immune system in cancer. Ann Oncol [Internet]. 2012 Sep 1 [cited 2019 Feb 4];23(suppl 8):viii6–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22918931

6. Allard B, Aspeslagh S, Garaud S, Dupont FA, Solinas C, Kok M, et al. Immuno-oncology-101: overview of major concepts and translational perspectives. Semin Cancer Biol [Internet]. 2018 Oct 1 [cited 2019 Feb 4];52:1–11. Available from: https://www.sciencedirect.com/science/article/pii/S1044579X1730233X

7. Yang Y. Cancer immunotherapy: harnessing the immune system to battle cancer. J Clin Invest [Internet]. 2015 Sep 1 [cited 2019 Nov 6];125(9):3335–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26325031

8. European Medicines Agency | [Internet]. [cited 2019 Nov 10]. Available from: https://www.ema.europa.eu/en

9. Martin-Liberal J, Hierro C, Ochoa de Olza M, Rodon J. Immuno-Oncology: The Third Paradigm in Early Drug Development. Target Oncol [Internet]. 2017 Apr 20 [cited 2019 Feb 4];12(2):125–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27995439

10. Dranitsaris G, Zhu X, Adunlin G, Vincent MD. Cost effectiveness vs. affordability in the age of immuno-oncology cancer drugs. Expert Rev Pharmacoecon Outcomes Res [Internet]. 2018 Jul 4 [cited 2019 Feb 4];18(4):351–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29681201

11. Kudrin A. Reimbursement challenges with cancer immunotherapeutics. Hum Vaccin Immunother [Internet]. 2012 Sep [cited 2019 Nov 6];8(9):1326–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22894969

12. Lugović-Mihić L, Ćesić D, Vuković P, Novak Bilić G, Šitum M, Špoljar S. Melanoma Development: Current Knowledge on Melanoma Pathogenesis. Acta Dermatovenerol Croat [Internet]. 2019 Sep [cited 2019 Nov 6];27(3):163–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31542060

13. Prado G, Svoboda RM, Rigel DS. What's New in Melanoma. Dermatol Clin [Internet]. 2019 Apr [cited 2019 Nov 6];37(2):159–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30850038

14. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. In Vivo [Internet]. [cited 2019 Nov 6];28(6):1005–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25398793

15. Krensel M, Schäfer I, Augustin M. Cost-of-illness of melanoma in Europe - a modelling approach. J Eur Acad Dermatology Venereol [Internet]. 2019 Mar [cited 2019 Nov 6];33:34–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30811699

16. PDQ Adult Treatment Editorial Board. Melanoma Treatment (PDQ®): Health Professional Version [Internet]. PDQ Cancer Information Summaries. 2002 [cited 2019 Oct 6]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26389469

17. Almutairi AR, Alkhatib NS, Oh M, Curiel-Lewandrowski C, Babiker HM, Cranmer LD, et al. Economic Evaluation of Talimogene Laherparepvec Plus Ipilimumab Combination Therapy vs Ipilimumab Monotherapy in Patients With Advanced Unresectable Melanoma. JAMA Dermatology [Internet]. 2019 Jan 1 [cited 2019 Nov 6];155(1):22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30477000

18. Leonardi GC, Falzone L, Salemi R, Zanghì A, Spandidos DA, Mccubrey JA, et al. Cutaneous melanoma: From pathogenesis to therapy (Review). Int J Oncol [Internet]. 2018 Apr [cited 2019 Nov 6];52(4):1071–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29532857

19. Marconcini R, Spagnolo F, Stucci LS, Ribero S, Marra E, De Rosa F, et al. NoneCurrent status and perspectives in immunotherapy for metastatic melanoma. Oncotarget [Internet]. 2017 Dec 28 [cited 2019 Nov 6];9(15):12452–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29552325

20. Conry RM, Westbrook B, McKee S, Norwood TG. Talimogene laherparepvec: First in class oncolytic virotherapy. Hum Vaccin Immunother [Internet]. 2018 [cited 2019 Nov 6];14(4):839–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29420123

21. Rabbie R, Ferguson P, Molina-Aguilar C, Adams DJ, Robles-Espinoza CD. Melanoma subtypes: genomic profiles, prognostic molecular markers and therapeutic possibilities. J Pathol [Internet]. 2019 Apr [cited 2019 Nov 11];247(5):539–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30511391

22. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 Blockade: New Immunotherapeutic Modalities with Durable Clinical Benefit in Melanoma Patients. Clin Cancer Res [Internet]. 2013 Oct 1 [cited 2019 Nov 11];19(19):5300–9. Available from: http://clincancerres.aacrjournals.org/cgi/doi/10.1158/1078-0432.CCR-13-0143

23. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ [Internet]. 1996 Jan 13 [cited 2019 Nov 6];312(7023):71–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8555924

24. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine - new approaches and challenges. Acta Inform Med [Internet]. 2008 [cited 2019 Nov 6];16(4):219–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24109156

25. Greenhalgh T. How to read a paper. Getting your bearings (deciding what the paper is about). BMJ [Internet]. 1997 Jul 26 [cited 2019 Nov 6];315(7102):243–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9253275

26. Kabisch M, Ruckes C, Seibert-Grafe M, Blettner M. Randomized controlled trials: part 17 of a series on evaluation of scientific publications. Dtsch Arztebl Int [Internet]. 2011 Sep [cited 2019 Nov 6];108(39):663–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22013494

27. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? Can J Surg [Internet]. 2010 Oct [cited 2019 Nov 6];53(5):345–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20858381

28. Anagnostou V, Yarchoan M, Hansen AR, Wang H, Verde F, Sharon E, et al. Immuno-oncology Trial Endpoints: Capturing Clinically Meaningful Activity. Clin Cancer Res [Internet]. 2017 Sep 1 [cited 2019 Nov 6];23(17):4959–69. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28864724

29. Borcoman E, Nandikolla A, Long G, Goel S, Le Tourneau C. Patterns of Response and Progression to Immunotherapy. Am Soc Clin Oncol Educ book Am Soc Clin Oncol Annu Meet [Internet]. 2018 May 23 [cited 2019 Nov 6];38(38):169–78. Available from: http://ascopubs.org/doi/10.1200/EDBK_200643

30. Martin-Liberal J, Hierro C, Ochoa de Olza M, Rodon J. Immuno-Oncology: The Third Paradigm in Early Drug Development. Target Oncol [Internet]. 2017 Apr 20 [cited 2019 Nov 6];12(2):125–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27995439

31. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspect Clin Res [Internet]. 2011 Oct [cited 2019 Nov 6];2(4):137–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22145124

32. Drummond M, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford University Press; 2015.

33. Bae J-M. Value-based medicine: concepts and application. Epidemiol Health [Internet]. 2015 [cited 2019 Nov 6];37:e2015014. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25773441

34. Abed I. The approval process of medicines in Europe. Med Writ. 2014;23(2):117–21.

35. Luce BR, Drummond M, Jönsson B, Neumann PJ, Schwartz JS, Siebert U, et al. EBM, HTA, and CER: clearing the confusion. Milbank Q [Internet]. 2010 Jun [cited 2019 Nov 6];88(2):256–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20579285

36. Organization - EUnetHTA [Internet]. [cited 2019 Oct 9]. Available from: https://eunethta.eu/about-eunethta/organization/

37. Authorisation of medicines | European Medicines Agency [Internet]. [cited 2019 Oct 9]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

38. Opportunity Cost Definition [Internet]. [cited 2019 Nov 7]. Available from: https://www.investopedia.com/terms/o/opportunitycost.asp

39. Perkins D. Principles of health economics including: the notions of scarcity, supply and demand,

distinctions between need and demand, opportunity cost, discounting, time horizons, margins, efficiency and equity | Health Knowledge [Internet]. 2017 [cited 2019 Nov 7]. Available from: https://www.healthknowledge.org.uk/public-health-textbook/medical-sociology-policy-economics/4d-health-economics/principles-he

40. Arenas-Guzman R, Tosti A, Hay R, Haneke E, National Institute for Clinical Excellence. Pharmacoeconomics - an aid to better decision-making. J Eur Acad Dermatology Venereol [Internet]. 2005 Sep [cited 2019 Nov 7];19(s1):34–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16120204

41. Rascati KL. Essentials of pharmacoeconomics. Second Edi. Essentials of Pharmacoeconomics: Second Edition. 2013. 1–295 p.

42. Hiligsmann M, John D, Al Ahdab OG, Li H. Pharmacoeconomic Analyses and Modeling. Clin Pharm Educ Pract Res [Internet]. 2019 Jan 1 [cited 2019 Nov 7];261–75. Available from: https://www.sciencedirect.com/science/article/pii/B9780128142769000180

43. Perkins D. Techniques of economic appraisal (including cost-effectiveness analysis and modelling, cost-utility analysis, option appraisal and cost-benefit analysis, the measurement of health benefits in terms of QALYs and related measures e.g. DALYs) | Health Knowledge [Internet]. 2017 [cited 2019 Nov 7]. Available from: https://www.healthknowledge.org.uk/public-health-textbook/medical-sociology-policy-economics/4d-health-economics/economic-appraisal

44. Ryder HF, McDonough C, Tosteson ANA, Lurie JD. Decision Analysis and Cost-effectiveness Analysis. Semin Spine Surg [Internet]. 2009 Dec [cited 2019 Nov 7];21(4):216–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23966758

45. Discount Rate Definition [Internet]. [cited 2019 Nov 7]. Available from: https://www.investopedia.com/terms/d/discountrate.asp

46. Ofman JJ, Sullivan SD, Neumann PJ, Chiou C-F, Henning JM, Wade SW, et al. Examining the Value and Quality of Health Economic Analyses: Implications of Utilizing the QHES. J Manag Care Pharm [Internet]. 2003 Jan [cited 2019 Nov 7];9(1):53–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14613362

47. Lange A, Prenzler A, Frank M, Kirstein M, Vogel A, von der Schulenburg JM. A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer. Eur J Cancer [Internet]. 2014 Jan [cited 2019 Sep 30];50(1):40–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24011538

48. Miguel LS, Lopes FV, Pinheiro B, Wang J, Xu R, Pellissier J, et al. Cost Effectiveness of Pembrolizumab for Advanced Melanoma Treatment in Portugal. Value Heal [Internet]. 2017 Sep [cited 2019 Sep 30];20(8):1065–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28964438

49. Wang J, Chmielowski B, Pellissier J, Xu R, Stevinson K, Liu FX. Cost-Effectiveness of Pembrolizumab Versus Ipilimumab in Ipilimumab-Naïve Patients with Advanced Melanoma in the United States. J Manag Care Spec Pharm [Internet]. 2017 Feb [cited 2019 Sep 30];23(2):184–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28125365

50. Meng Y, Hertel N, Ellis J, Morais E, Johnson H, Philips Z, et al. The cost-effectiveness of nivolumab

monotherapy for the treatment of advanced melanoma patients in England. Eur J Heal Econ [Internet]. 2018 Nov 9 [cited 2019 Sep 30];19(8):1163–72. Available from: http://link.springer.com/10.1007/s10198-018-0964-4

51. Bohensky MA, Pasupathi K, Gorelik A, Kim H, Harrison JP, Liew D. A Cost-Effectiveness Analysis of Nivolumab Compared with Ipilimumab for the Treatment of BRAF Wild-Type Advanced Melanoma in Australia. Value Heal [Internet]. 2016 Dec [cited 2019 Sep 30];19(8):1009–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1098301516305046

52. Curl P, Vujic I, van 't Veer LJ, Ortiz-Urda S, Kahn JG. Cost-Effectiveness of Treatment Strategies for BRAF-Mutated Metastatic Melanoma. Slominski AT, editor. PLoS One [Internet]. 2014 Sep 8 [cited 2019 Sep 30];9(9):e107255. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25198196

53. Tarhini A, Benedict A, McDermott D, Rao S, Ambavane A, Gupte-Singh K, et al. Sequential treatment approaches in the management of *BRAF* wild-type advanced melanoma: a cost–effectiveness analysis. Immunotherapy [Internet]. 2018 Oct [cited 2019 Sep 30];10(14):1241–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30175642

54. Kohn CG, Zeichner SB, Chen Q, Montero AJ, Goldstein DA, Flowers CR. Cost-Effectiveness of Immune Checkpoint Inhibition in *BRAF* Wild-Type Advanced Melanoma. J Clin Oncol [Internet]. 2017 Apr 10 [cited 2019 Sep 30];35(11):1194–202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28221865

55. Oh A, Tran DM, McDowell LC, Keyvani D, Barcelon JA, Merino O, et al. Cost-Effectiveness of Nivolumab-Ipilimumab Combination Therapy Compared with Monotherapy for First-Line Treatment of Metastatic Melanoma in the United States. J Manag Care Spec Pharm [Internet]. 2017 Jun [cited 2019 Sep 30];23(6):653–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28530525

56. Pike E, Hamidi V, Saeterdal I, Odgaard-Jensen J, Klemp M. Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting. BMJ Open [Internet]. 2017 Aug 21 [cited 2019 Oct 12];7(8):e014880. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28827234

57. Johnston KM, McPherson E, Osenenko K, Vergidis J, Levy AR, Peacock S. Cost–effectiveness of therapies for melanoma. Expert Rev Pharmacoecon Outcomes Res [Internet]. 2015 Mar 4 [cited 2019 Sep 30];15(2):229–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25703441

58. Sarfaty M, Hall PS, Chan KKW, Virik K, Leshno M, Gordon N, et al. Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer. Eur Urol [Internet]. 2018 Jul [cited 2019 Sep 30];74(1):57–62. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0302283818301829

59. Kovic B, Xie F. Economic Evaluation of Bevacizumab for the First-Line Treatment of Newly Diagnosed Glioblastoma Multiforme. J Clin Oncol [Internet]. 2015 Jul 10 [cited 2019 Sep 30];33(20):2296–302. Available from: http://ascopubs.org/doi/10.1200/JCO.2014.59.7245

60. Petitjean A, Smith-Palmer J, Valentine W, Tehard B, Roze S. Cost-effectiveness of bevacizumab plus paclitaxel versus paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer in specialist oncology centers in France. BMC Cancer [Internet]. 2019 Dec 11 [cited 2019 Sep 30];19(1):140.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/30744578

61. Kongsakon R, Lochid-amnuay S, Kapol N, Pattanaprateep O. From Research to Policy Implementation: Trastuzumab in Early-Stage Breast Cancer Treatment in Thailand. Value Heal Reg Issues [Internet]. 2019 May [cited 2019 Sep 30];18:47–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30428405

62. Seferina SC, Ramaekers BLT, de Boer M, Dercksen MW, Berkmortel F van den, van Kampen RJW, et al. Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: A study of the Southeast Netherlands Breast Cancer Consortium. Oncotarget [Internet]. 2017 Oct 3 [cited 2019 Sep 30];8(45):79223–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29108301

63. Leung HWC, Chan ALF, Muo C-H, Leung JH. Cost-effectiveness of pertuzumab combined with trastuzumab and docetaxel as a first-line treatment for HER-2 positive metastatic breast cancer. Expert Rev Pharmacoecon Outcomes Res [Internet]. 2018 Mar 4 [cited 2019 Sep 30];18(2):207–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28965422

64. Diaby V, Ali AA, Williams KJ, Ezendu K, Soto-Perez-de-Celis E, Chavarri-Guerra Y, et al. Economic evaluation of sequencing strategies in HER2-positive metastatic breast cancer in Mexico: a contrast between public and private payer perspectives. Breast Cancer Res Treat [Internet]. 2017 Dec 24 [cited 2019 Sep 30];166(3):951–63. Available from: http://link.springer.com/10.1007/s10549-017-4473-4

65. Ansaripour A, Uyl-de Groot CA, Redekop WK. Adjuvant Trastuzumab Therapy for Early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy. Pharmacoeconomics [Internet]. 2018 Jan 9 [cited 2019 Sep 30];36(1):91–103. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28795341

66. Clarke CS, Hunter RM, Shemilt I, Serra-Sastre V. Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective. Wilson FA, editor. PLoS One [Internet]. 2017 Mar 1 [cited 2019 Sep 30];12(3):e0172731. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28248984

67. van Kampen RJW, Ramaekers BLT, Lobbezoo DJA, de Boer M, Dercksen MW, van den Berkmortel F, et al. Real-world and trial-based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients: a study of the Southeast Netherlands Breast Cancer Consortium. Eur J Cancer [Internet]. 2017 Jul [cited 2019 Sep 30];79:238–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28245951

68. Diaby V, Adunlin G, Ali AA, Zeichner SB, de Lima Lopes G, Kohn CG, et al. Cost-effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States. Breast Cancer Res Treat [Internet]. 2016 Nov 21 [cited 2019 Sep 30];160(1):187–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27654970

69. Le QA, Bae YH, Kang JH. Cost-effectiveness analysis of trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2): positive advanced breast cancer. Breast Cancer Res Treat [Internet]. 2016 Oct 29 [cited 2019 Sep 30];159(3):565–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27572338

70. Leung W, Kvizhinadze G, Nair N, Blakely T. Adjuvant Trastuzumab in HER2-Positive Early Breast Cancer by Age and Hormone Receptor Status: A Cost-Utility Analysis. Holmberg L, editor. PLOS Med [Internet]. 2016 Aug 9 [cited 2019 Sep 30];13(8):e1002067. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27504960

71. Lang H-C, Chen H-W, Chiou T-J, Chan ALF. The real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu-positive early breast cancer in Taiwan. J Med Econ [Internet]. 2016 Oct 2 [cited 2019 Nov 12];19(10):923–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27135256

72. Beauchemin C, Letarte N, Mathurin K, Yelle L, Lachaine J. A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada. J Med Econ [Internet]. 2016 Jun 2 [cited 2019 Sep 30];19(6):619–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26850287

73. Durkee BY, Qian Y, Pollom EL, King MT, Dudley SA, Shaffer JL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer. J Clin Oncol [Internet]. 2016 Mar 20 [cited 2019 Sep 30];34(9):902–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26351332

74. Kourlaba G, Rapti V, Alexopoulos A, Relakis J, Koumakis G, Chatzikou M, et al. Everolimus plus exemestane versus bevacizumab-based chemotherapy for second-line treatment of hormone receptor-positive metastatic breast cancer in Greece: An economic evaluation study. BMC Health Serv Res [Internet]. 2015 Dec 5 [cited 2019 Sep 30];15(1):307. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26239115

75. Aboutorabi A, Hadian M, Ghaderi H, Salehi M, Ghiasipour M. Cost-Effectiveness Analysis of Trastuzumab in the Adjuvant Treatment for Early Breast Cancer. Glob J Health Sci [Internet]. 2014 Aug 14 [cited 2019 Sep 30];7(1):98–106. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25560346

76. Chicaíza-Becerra L, García-Molina M, Gamboa O, Castañeda-Orjuela C. ErbB2+ metastatic breast cancer treatment after progression on trastuzumab: a cost-effectiveness analysis for a developing country. Rev Salud Publica (Bogota) [Internet]. [cited 2019 Sep 30];16(2):270–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25383500

77. Attard CL, Pepper AN, Brown ST, Thompson MF, Thuresson P-O, Yunger S, et al. Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. J Med Econ [Internet]. 2015 Mar 4 [cited 2019 Sep 30];18(3):173–88. Available from: http://www.tandfonline.com/doi/full/10.3111/13696998.2014.979938

78. Candon D, Healy J, Crown J. Modelling the cost-effectiveness of adjuvant lapatinib for early-stage breast cancer. Acta Oncol (Madr) [Internet]. 2014 Feb 14 [cited 2019 Sep 30];53(2):201–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24125103

79. Refaat T, Choi M, Gaber G, Kiel K, Mehta M, Gradishar W, et al. Markov Model and Cost-Effectiveness Analysis of Bevacizumab in HER2-Negative Metastatic Breast Cancer. Am J Clin Oncol [Internet]. 2014 Oct [cited 2019 Sep 30];37(5):480–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23388565

80. Geisler J, Klag N, Walter AC, Sheely K, Manahan KJ. Is the routine use of bevacizumab in the treatment

of women with advanced or recurrent cancer of the cervix sustainable? Clin Outcomes Res [Internet]. 2016 Jun [cited 2019 Sep 30];287. Available from: https://www.dovepress.com/is-the-routine-use-of-bevacizumab-in-the-treatment-of-women-with-advan-peer-reviewed-article-CEOR

81. Minion LE, Bai J, Monk BJ, Robin Keller L, Ramez EN, Forde GK, et al. A Markov model to evaluate cost-effectiveness of antiangiogenesis therapy using bevacizumab in advanced cervical cancer. Gynecol Oncol [Internet]. 2015 Jun [cited 2019 Sep 30];137(3):490–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825815006769

82. Phippen NT, Leath CA, Havrilesky LJ, Barnett JC. Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: Is it cost-effective? Gynecol Oncol [Internet]. 2015 Jan [cited 2019 Sep 30];136(1):43–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0090825814014164

83. Sherman SK, Lange JJ, Dahdaleh FS, Rajeev R, Gamblin TC, Polite BN, et al. Cost-effectiveness of Maintenance Capecitabine and Bevacizumab for Metastatic Colorectal Cancer. JAMA Oncol [Internet]. 2019 Feb 1 [cited 2019 Sep 30];5(2):236. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30489611

84. Xu Y, Hay JW, Barzi A. Impact of drug substitution on cost of care: an example of economic analysis of cetuximab versus panitumumab. Cost Eff Resour Alloc [Internet]. 2018 Dec 12 [cited 2019 Sep 30];16(1):30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30459532

85. Chu JN, Choi J, Ostvar S, Torchia JA, Reynolds KL, Tramontano A, et al. Cost-effectiveness of immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer. Cancer [Internet]. 2019 Jan 15 [cited 2019 Sep 30];125(2):278–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30343509

86. Graham CN, Christodoulopoulou A, Knox HN, Sabatelli L, Hechmati G, Garawin T, et al. A within-trial cost-effectiveness analysis of panitumumab compared with bevacizumab in the first-line treatment of patients with wild-type *RAS* metastatic colorectal cancer in the US. J Med Econ [Internet]. 2018 Nov 2 [cited 2019 Sep 30];21(11):1075–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30091652

87. Uyl-de Groot CA, van Rooijen EM, Punt CJA, Pescott CP. Real-world cost-effectiveness of cetuximab in the third-line treatment of metastatic colorectal cancer based on patient chart review in the Netherlands. Health Econ Rev [Internet]. 2018 Dec 17 [cited 2019 Sep 30];8(1):13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30019286

88. Tikhonova IA, Huxley N, Snowsill T, Crathorne L, Varley-Campbell J, Napier M, et al. Economic Analysis of First-Line Treatment with Cetuximab or Panitumumab for RAS Wild-Type Metastatic Colorectal Cancer in England. Pharmacoeconomics [Internet]. 2018 Jul 1 [cited 2019 Sep 30];36(7):837–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29498000

89. Wu B, Yao Y, Zhang K, Ma X. RAS testing and cetuximab treatment for metastatic colorectal cancer: a cost-effectiveness analysis in a setting with limited health resources. Oncotarget [Internet]. 2017 Sep 19 [cited 2019 Sep 30];8(41). Available from: http://www.oncotarget.com/fulltext/17029

90. Ungari AQ, Pereira LRL, Nunes AA, Peria FM. Cost-effectiveness analysis of XELOX versus XELOX

plus bevacizumab for metastatic colorectal cancer in a public hospital school. BMC Cancer [Internet]. 2017 Dec 17 [cited 2019 Sep 30];17(1):691. Available from: http://bmccancer.biomedcentral.com/articles/10.1186/s12885-017-3679-5

91. Goldstein DA, Chen Q, Ayer T, Chan KKW, Virik K, Hammerman A, et al. Bevacizumab for Metastatic Colorectal Cancer: A Global Cost-Effectiveness Analysis. Oncologist [Internet]. 2017 Jun [cited 2019 Sep 30];22(6):694–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28592621

92. Carvalho AC, Leal F, Sasse AD. Cost-effectiveness of cetuximab and panitumumab for chemotherapy-refractory metastatic colorectal cancer. Souglakos J, editor. PLoS One [Internet]. 2017 Apr 12 [cited 2019 Sep 30];12(4):e0175409. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28403233

93. Franken MD, van Rooijen EM, May AM, Koffijberg H, van Tinteren H, Mol L, et al. Cost-effectiveness of capecitabine and bevacizumab maintenance treatment after first-line induction treatment in metastatic colorectal cancer. Eur J Cancer [Internet]. 2017 Apr [cited 2019 Sep 30];75:204–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28237866

94. Rivera F, Valladares M, Gea S, López-Martínez N. Cost-effectiveness analysis in the Spanish setting of the PEAK trial of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer. J Med Econ [Internet]. 2017 Jun 3 [cited 2019 Sep 30];20(6):574–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28107090

95. Parikh RC, Du XL, Robert MO, Lairson DR. Cost-Effectiveness of Treatment Sequences of Chemotherapies and Targeted Biologics for Elderly Metastatic Colorectal Cancer Patients. J Manag Care Spec Pharm [Internet]. 2017 Jan [cited 2019 Sep 30];23(1):64–73. Available from: http://www.jmcp.org/doi/10.18553/jmcp.2017.23.1.64

96. Zhou J, Zhao R, Wen F, Zhang P, Tang R, Chen H, et al. Economic evaluation study (CHEER-compliant). Medicine (Baltimore) [Internet]. 2016 Jul [cited 2019 Sep 30];95(27):e3762. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27399059

97. Riesco-Martínez MC, Berry SR, Ko Y-J, Mittmann N, Giotis A, Lien K, et al. Cost-Effectiveness Analysis of Different Sequences of the Use of Epidermal Growth Factor Receptor Inhibitors for Wild-Type *KRAS* Unresectable Metastatic Colorectal Cancer. J Oncol Pract [Internet]. 2016 Jun [cited 2019 Sep 30];12(6):e710–23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27143148

98. Matter-Walstra K, Schwenkglenks M, Betticher D, von Moos R, Dietrich D, Baertschi D, et al. Bevacizumab Continuation Versus Treatment Holidays After First-Line Chemotherapy With Bevacizumab in Patients With Metastatic Colorectal Cancer: A Health Economic Analysis of a Randomized Phase 3 Trial (SAKK 41/06). Clin Colorectal Cancer [Internet]. 2016 Dec [cited 2019 Sep 30];15(4):314-320.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27117056

99. Graham CN, Maglinte GA, Schwartzberg LS, Price TJ, Knox HN, Hechmati G, et al. Economic Analysis of Panitumumab Compared With Cetuximab in Patients With Wild-type KRAS Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy. Clin Ther [Internet]. 2016 Jun [cited 2019 Sep 30];38(6):1376–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27085587

100. Shankaran V, Ortendahl JD, Purdum AG, Bolinder B, Anene AM, Sun GH, et al. Cost-Effectiveness of Cetuximab as First-line Treatment for Metastatic Colorectal Cancer in the United States. Am J Clin Oncol [Internet]. 2015 Sep [cited 2019 Sep 30];41(1):1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26398184

101. Tabatabaei M, Ashrafi F, Aslani A, Davari M, Maracy M. Cost-effectiveness analysis of cetuximab in treatment of metastatic colorectal cancer in Iranian pharmaceutical market. Int J Prev Med [Internet]. 2015 [cited 2019 Sep 30];6(1):63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26288707

102. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, El-Rayes BF, et al. First- and Second-Line Bevacizumab in Addition to Chemotherapy for Metastatic Colorectal Cancer: A United States–Based Cost-Effectiveness Analysis. J Clin Oncol [Internet]. 2015 Apr 1 [cited 2019 Sep 30];33(10):1112–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25691669

103. Graham CN, Hechmati G, Hjelmgren J, de Liège F, Lanier J, Knox H, et al. Cost-effectiveness analysis of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer. Eur J Cancer [Internet]. 2014 Nov [cited 2019 Sep 30];50(16):2791–801. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25219451

104. Ewara EM, Zaric GS, Welch S, Sarma S. Cost-effectiveness of first-line treatments for patients with KRAS wild-type metastatic colorectal cancer. Curr Oncol [Internet]. 2014 May 16 [cited 2019 Sep 30];21(4):541. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25089105

105. Carter HE, Zannino D, John Simes R, Schofield DJ, Howard K, Zalcberg JR, et al. The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: Results from the Australasian phase III MAX study. Eur J Cancer [Internet]. 2014 Feb [cited 2019 Sep 30];50(3):535–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24215848

106. Ruiz-Millo O, Albert-Mari A, Sendra-Garcia A, Jimenez-Torres NV. Comparative cost-effectiveness of bevacizumab-irinotecan-fluorouracil versus irinotecan-fluorouracil in first-line metastatic colorectal cancer. J Oncol Pharm Pract [Internet]. 2014 Oct 31 [cited 2019 Sep 30];20(5):341–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24177355

107. Barrington DA, Dilley SE, Smith HJ, Straughn JM. Pembrolizumab in advanced recurrent endometrial cancer: A cost-effectiveness analysis. Gynecol Oncol [Internet]. 2019 May [cited 2019 Sep 30];153(2):381–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30808517

108. Janmaat VT, Bruno MJ, Polinder S, Lorenzen S, Lordick F, Peppelenbosch MP, et al. Cost-Effectiveness of Cetuximab for Advanced Esophageal Squamous Cell Carcinoma. McLaughlin-Drubin M, editor. PLoS One [Internet]. 2016 Apr 21 [cited 2019 Sep 30];11(4):e0153943. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27100871

109. Saito S, Muneoka Y, Ishikawa T, Akazawa K. Cost-effectiveness of Paclitaxel + Ramucirumab Combination Therapy for Advanced Gastric Cancer Progressing After First-line Chemotherapy in Japan. Clin Ther [Internet]. 2017 Dec [cited 2019 Sep 30];39(12):2380–8. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/29175097

110. Kimura M, Usami E, Teramachi H, Yoshimura T. Cost-effectiveness and safety of ramucirumab plus paclitaxel chemotherapy in the treatment of advanced and recurrent gastric cancer. J Oncol Pharm Pract [Internet]. 2018 Sep 24 [cited 2019 Sep 30];24(6):403–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28436252

111. Lam SW, Wai M, Lau JE, McNamara M, Earl M, Udeh B. Cost-Effectiveness Analysis of Second-Line Chemotherapy Agents for Advanced Gastric Cancer. Pharmacother J Hum Pharmacol Drug Ther [Internet]. 2017 Jan [cited 2019 Sep 30];37(1):94–103. Available from: http://doi.wiley.com/10.1002/phar.1870

112. Hirschmann A, Lupatsch JE, Schwenkglenks M, Panje CM, Matter-Walstra K, Espeli V, et al. Cost-effectiveness of nivolumab in the treatment of head and neck cancer. Oral Oncol [Internet]. 2018 Dec [cited 2019 Sep 30];87:104–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30527224

113. Kim H, Vargo JA, Beriwal S, Clump DA, Ohr JP, Ferris RL, et al. Cost-effectiveness analysis of salvage therapies in locoregional previously irradiated head and neck cancer. Head Neck [Internet]. 2018 Mar 14 [cited 2019 Sep 30]; Available from: http://doi.wiley.com/10.1002/hed.25142

114. Tringale KR, Carroll KT, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness Analysis of Nivolumab for Treatment of Platinum-Resistant Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. JNCI J Natl Cancer Inst [Internet]. 2018 May 1 [cited 2019 Sep 30];110(5):479–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29126314

115. Ward MC, Shah C, Adelstein DJ, Geiger JL, Miller JA, Koyfman SA, et al. Cost-effectiveness of nivolumab for recurrent or metastatic head and neck cancer☆. Oral Oncol [Internet]. 2017 Nov [cited 2019 Sep 30];74:49–55. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1368837517302968

116. Zargar M, McFarlane T, Chan KKW, Wong WWL. Cost-Effectiveness of Nivolumab in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma. Oncologist [Internet]. 2018 Feb [cited 2019 Sep 30];23(2):225–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29021380

117. van der Linden N, van Gils CWM, Pescott CP, Buter J, Vergeer MR, Groot CAU. Real-world cost-effectiveness of cetuximab in locally advanced squamous cell carcinoma of the head and neck. Eur Arch Oto-Rhino-Laryngology [Internet]. 2015 Aug 19 [cited 2019 Sep 30];272(8):2007–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24943191

118. Nam J, Milenkovski R, Yunger S, Geirnaert M, Paulson K, Seftel M. Economic evaluation of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia. J Med Econ [Internet]. 2018 Jan 2 [cited 2019 Sep 30];21(1):47–59. Available from: https://www.tandfonline.com/doi/full/10.1080/13696998.2017.1372230

119. Sinha R, Redekop WK. Cost-Effectiveness of Ibrutinib Compared With Obinutuzumab With Chlorambucil in Untreated Chronic Lymphocytic Leukemia Patients With Comorbidities in the United Kingdom. Clin Lymphoma Myeloma Leuk [Internet]. 2018 Feb [cited 2019 Sep 30];18(2):e131–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29398648

120. Casado LF, Hernández JÁ, Jarque I, Echave M, Casado MA, Castro A. Cost-utility analysis of idelalisib in combination with rituximab in relapsed or refractory chronic lymphocytic leukaemia. Eur J Haematol [Internet]. 2018 Mar [cited 2019 Sep 30];100(3):264–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29226472

121. Paquete AT, Miguel LS, Becker U, Pereira C, Pinto CG. Cost-Effectiveness Analysis of Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukaemia in Portuguese Patients who are Unsuitable for Full-Dose Fludarabine-Based Therapy. Appl Health Econ Health Policy [Internet]. 2017 Aug 24 [cited 2019 Sep 30];15(4):501–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28342061

122. Blommestein HM, de Groot S, Aarts MJ, Vemer P, de Vries R, van Abeelen AFM, et al. Cost-effectiveness of obinutuzumab for chronic lymphocytic leukaemia in The Netherlands. Leuk Res [Internet]. 2016 Nov [cited 2019 Sep 30];50:37–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27657652

123. Becker U, Briggs AH, Moreno SG, Ray JA, Ngo P, Samanta K. Cost-Effectiveness Model for Chemoimmunotherapy Options in Patients with Previously Untreated Chronic Lymphocytic Leukemia Unsuitable for Full-Dose Fludarabine-Based Therapy. Value Heal [Internet]. 2016 Jun [cited 2019 Sep 30];19(4):374–82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27325329

124. Soini E, Hautala A, Poikonen E, Becker U, Kyttälä M, Martikainen J. Cost-effectiveness of First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable. Clin Ther [Internet]. 2016 Apr [cited 2019 Sep 30];38(4):889-904.e14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26970696

125. Müller D, Fischer K, Kaiser P, Eichhorst B, Walshe R, Reiser M, et al. Cost-effectiveness of rituximab in addition to fludarabine and cyclophosphamide (R-FC) for the first-line treatment of chronic lymphocytic leukemia. Leuk Lymphoma [Internet]. 2016 May 3 [cited 2019 Sep 30];57(5):1130–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26584689

126. Herring W, Pearson I, Purser M, Nakhaipour HR, Haiderali A, Wolowacz S, et al. Cost Effectiveness of Ofatumumab Plus Chlorambucil in First-Line Chronic Lymphocytic Leukaemia in Canada. Pharmacoeconomics [Internet]. 2016 Jan 30 [cited 2019 Sep 30];34(1):77–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26518293

127. Mandrik O, Corro Ramos I, Knies S, Al M, Severens J (Hans). Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia in Ukraine. Cancer Manag Res [Internet]. 2015 Aug [cited 2019 Sep 30];7:279. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26345331

128. Adena M, Houltram J, Mulligan SP, Todd C, Malanos G. Modelling the Cost Effectiveness of Rituximab in Chronic Lymphocytic Leukaemia in First-Line Therapy and Following Relapse. Pharmacoeconomics [Internet]. 2014 Feb 18 [cited 2019 Sep 30];32(2):193–207. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24442832

129. Delea TE, Amdahl J, Boyko D, Hagiwara M, Zimmerman ZF, Franklin JL, et al. Cost-effectiveness of blinatumomab versus salvage chemotherapy in relapsed or refractory Philadelphia-chromosome-negative

B-precursor acute lymphoblastic leukemia from a US payer perspective. J Med Econ [Internet]. 2017 Sep 2 [cited 2019 Sep 30];20(9):911–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28631497

130. Roth JA, Sullivan SD, Lin VW, Bansal A, Purdum AG, Navale L, et al. Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States. J Med Econ [Internet]. 2018 Dec 2 [cited 2019 Sep 30];21(12):1238–45. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30260711

131. Chen Q, Staton AD, Ayer T, Goldstein DA, Koff JL, Flowers CR. Exploring the potential cost-effectiveness of precision medicine treatment strategies for diffuse large B-cell lymphoma. Leuk Lymphoma [Internet]. 2018 Jul 3 [cited 2019 Sep 30];59(7):1700–9. Available from: https://www.tandfonline.com/doi/full/10.1080/10428194.2017.1390230

132. Khor S, Beca J, Krahn M, Hodgson D, Lee L, Crump M, et al. Real world costs and cost-effectiveness of Rituximab for diffuse large B-cell lymphoma patients: a population-based analysis. BMC Cancer [Internet]. 2014 Dec 12 [cited 2019 Sep 30];14(1):586. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25117912

133. Guzauskas GF, Masaquel A, Reyes C, Bernaards C, Krivasi T, Veenstra DL. Cost-effectiveness of obinutuzumab plus bendamustine followed by obinutuzumab monotherapy for the treatment of follicular lymphoma patients who relapse after or are refractory to a rituximab-containing regimen in the US. J Med Econ [Internet]. 2018 Oct 3 [cited 2019 Sep 30];21(10):960–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29898619

134. Prettyjohns M, Hoskin P, McNamara C, Linch D. The cost-effectiveness of immediate treatment or watch and wait with deferred chemotherapy for advanced asymptomatic follicular lymphoma. Br J Haematol [Internet]. 2018 Jan [cited 2019 Sep 30];180(1):52–9. Available from: http://doi.wiley.com/10.1111/bjh.14990

135. Sabater E, López-Guillermo A, Rueda A, Salar A, Oyagüez I, Collar JM. Cost-Effectiveness Analysis of Bendamustine Plus Rituximab as a First-Line Treatment for Patients with Follicular Lymphoma in Spain. Appl Health Econ Health Policy [Internet]. 2016 Aug 18 [cited 2019 Sep 30];14(4):465–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27090915

136. Prica A, Chan K, Cheung M. Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced-stage follicular lymphoma: A cost-effectiveness analysis. Cancer [Internet]. 2015 Aug 1 [cited 2019 Sep 30];121(15):2637–45. Available from: http://doi.wiley.com/10.1002/cncr.29372

137. Chen Q, Ayer T, Nastoupil LJ, Rose AC, Flowers CR. Comparing the Cost-Effectiveness of Rituximab Maintenance and Radioimmunotherapy Consolidation versus Observation Following First-Line Therapy in Patients with Follicular Lymphoma. Value Heal [Internet]. 2015 Mar [cited 2019 Sep 30];18(2):189–97. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1098301515000108

138. Blommestein HM, Issa DE, Pompen M, Ten Hoor G, Hogendoorn M, Joosten P, et al. Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: results of a population-based

study. Eur J Haematol [Internet]. 2014 May [cited 2019 Sep 30];92(5):398–406. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24400940

139. Delea TE, Sharma A, Grossman A, Eichten C, Fenton K, Josephson N, et al. Cost-effectiveness of brentuximab vedotin plus chemotherapy as frontline treatment of stage III or IV classical Hodgkin lymphoma. J Med Econ [Internet]. 2019 Feb 10 [cited 2019 Sep 30];22(2):117–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30375910

140. Huntington SF, von Keudell G, Davidoff AJ, Gross CP, Prasad SA. Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma. J Clin Oncol [Internet]. 2018 Nov 20 [cited 2019 Sep 30];36(33):3307–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30285558

141. Hui L, von Keudell G, Wang R, Zeidan AM, Gore SD, Ma X, et al. Cost-effectiveness analysis of consolidation with brentuximab vedotin for high-risk Hodgkin lymphoma after autologous stem cell transplantation. Cancer [Internet]. 2017 Oct 1 [cited 2019 Sep 30];123(19):3763–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28640385

142. Babashov V, Begen MA, Mangel J, Zaric GS. Economic evaluation of brentuximab vedotin for persistent Hodgkin lymphoma. Curr Oncol [Internet]. 2017 Feb 28 [cited 2019 Sep 30];24(1):6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28270727

143. Parker C, Woods B, Eaton J, Ma E, Selby R, Benson E, et al. Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma post-autologous stem cell transplant: a cost-effectiveness analysis in Scotland. J Med Econ [Internet]. 2017 Jan 2 [cited 2019 Sep 30];20(1):8–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27472034

144. van Keep M, Gairy K, Seshagiri D, Thilakarathne P, Lee D. Cost-effectiveness analysis of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (VR-CAP) in patients with previously untreated mantle cell lymphoma. BMC Cancer [Internet]. 2016 Dec 4 [cited 2019 Sep 30];16(1):598. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27488675

145. Dewilde S, Woods B, Castaigne J-G, Parker C, Dunlop W. Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales. J Med Econ [Internet]. 2014 Feb 13 [cited 2019 Sep 30];17(2):111–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24308372

146. Bullement A, Nathan P, Willis A, Amin A, Lilley C, Stapelkamp C, et al. Cost Effectiveness of Avelumab for Metastatic Merkel Cell Carcinoma. PharmacoEconomics - Open [Internet]. 2019 Sep 24 [cited 2019 Sep 30];3(3):377–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30680676

147. Zhang T, Wang S, Wan N, Zhang L, Zhang Z, Jiang J. Cost-effectiveness of Daratumumab-based Triplet Therapies in Patients With Relapsed or Refractory Multiple Myeloma. Clin Ther [Internet]. 2018 Jul [cited 2019 Sep 30];40(7):1122–39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30006069

148. Carlson JJ, Guzauskas GF, Chapman RH, Synnott PG, Liu S, Russo ET, et al. Cost-effectiveness of Drugs to Treat Relapsed/Refractory Multiple Myeloma in the United States. J Manag Care Spec Pharm [Internet].

2018 Jan [cited 2019 Sep 30];24(1):29–38. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29290170

149. Pelligra CG, Parikh K, Guo S, Chandler C, Mouro J, Abouzaid S, et al. Cost-effectiveness of Pomalidomide, Carfilzomib, and Daratumumab for the Treatment of Patients with Heavily Pretreated Relapsed–refractory Multiple Myeloma in the United States. Clin Ther [Internet]. 2017 Oct [cited 2019 Sep 30];39(10):1986-2005.e5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28967482

150. Ondhia U, Conter HJ, Owen S, Zhou A, Nam J, Singh S, et al. Cost-effectiveness of second-line atezolizumab in Canada for advanced non-small cell lung cancer (NSCLC). J Med Econ [Internet]. 2019 Jul 3 [cited 2019 Sep 30];22(7):625–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30836031

151. Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Ejzykowicz F, et al. Cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US. Curr Med Res Opin [Internet]. 2019 Jul 3 [cited 2019 Sep 30];35(7):1241–56. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30649973

152. Liao W, Huang J, Hutton D, Li Q. Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China. J Med Econ [Internet]. 2019 Apr 3 [cited 2019 Sep 30];22(4):344–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30646794

153. Chouaid C, Bensimon L, Clay E, Millier A, Levy-Bachelot L, Huang M, et al. Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France. Lung Cancer [Internet]. 2019 Jan [cited 2019 Sep 30];127:44–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30642550

154. Criss SD, Mooradian MJ, Sheehan DF, Zubiri L, Lumish MA, Gainor JF, et al. Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non–Small Cell Lung Cancer in the Context of the US Health Care System. JAMA Oncol [Internet]. 2019 Mar 1 [cited 2019 Sep 30];5(3):358. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30543349

155. Gao L, Li S-C. Modelled Economic Evaluation of Nivolumab for the Treatment of Second-Line Advanced or Metastatic Squamous Non-Small-Cell Lung Cancer in Australia Using Both Partition Survival and Markov Models. Appl Health Econ Health Policy [Internet]. 2019 Jun 10 [cited 2019 Sep 30];17(3):371–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30535675

156. Li X, Li W, Hou L. A Trial-Based Cost-Effectiveness Analysis of Bevacizumab and Chemotherapy Versus Chemotherapy Alone for Advanced Nonsquamous Non–Small-Cell Lung Cancer in China. Value Heal Reg Issues [Internet]. 2019 May [cited 2019 Sep 30];18:1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30412913

157. Georgieva M, da Silveira Nogueira Lima JP, Aguiar P, de Lima Lopes G, Haaland B. Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer. Lung Cancer [Internet].

2018 Oct [cited 2019 Sep 30];124:248–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30268469

158. Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Burke T. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. J Med Econ [Internet]. 2018 Dec 2 [cited 2019 Sep 30];21(12):1191–205. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30188231

159. Hu X, Hay JW. First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective. Lung Cancer [Internet]. 2018 Sep [cited 2019 Sep 30];123:166–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30089590

160. Shafrin J, Skornicki M, Brauer M, Villeneuve J, Lees M, Hertel N, et al. An exploratory case study of the impact of expanding cost-effectiveness analysis for second-line nivolumab for patients with squamous non-small cell lung cancer in Canada: Does it make a difference? Health Policy (New York) [Internet]. 2018 Jun [cited 2019 Sep 30];122(6):607–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29731176

161. Zheng H, Xie L, Zhan M, Wen F, Xu T, Li Q. Cost-effectiveness analysis of the addition of bevacizumab to chemotherapy as induction and maintenance therapy for metastatic non-squamous non-small-cell lung cancer. Clin Transl Oncol [Internet]. 2018 Mar 7 [cited 2019 Sep 30];20(3):286–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28785913

162. Aguiar PN, Perry LA, Penny-Dimri J, Babiker H, Tadokoro H, de Mello RA, et al. The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC. Ann Oncol [Internet]. 2017 Sep 1 [cited 2019 Sep 30];28(9):2256–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28633409

163. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics [Internet]. 2017 Aug 15 [cited 2019 Sep 30];35(8):831–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28620848

164. González García J, Gutiérrez Nicolás F, Nazco Casariego GJ, Valcárcel Nazco C, Batista López JN, Oramas Rodríguez J. Cost-effectiveness of pemetrexed in combination with cisplatin as first line treatment for patients with advanced non-squamous non-small-cell lung cancer in Spain. Farm Hosp [Internet]. 2017 Jan 1 [cited 2019 Sep 30];41(n01):3–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28045649

165. Matter-Walstra K, Schwenkglenks M, Aebi S, Dedes K, Diebold J, Pietrini M, et al. A Cost-Effectiveness Analysis of Nivolumab versus Docetaxel for Advanced Nonsquamous NSCLC Including PD-L1 Testing. J Thorac Oncol [Internet]. 2016 Nov [cited 2019 Sep 30];11(11):1846–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27311996

166. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, et al. Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States. J Med Econ [Internet]. 2017 Feb 3 [cited 2019 Sep 30];20(2):140–50. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/27571538

167. Goeree R, Villeneuve J, Goeree J, Penrod JR, Orsini L, Tahami Monfared AA. Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. J Med Econ [Internet]. 2016 Jun 2 [cited 2019 Sep 30];19(6):630–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26850122

168. Kumar G, Woods B, Hess LM, Treat J, Boye ME, Bryden P, et al. Cost-effectiveness of first-line induction and maintenance treatment sequences in non-squamous non-small cell lung cancer (NSCLC) in the U.S. Lung Cancer [Internet]. 2015 Sep [cited 2019 Sep 30];89(3):294–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26122345

169. Neyt M, Vlayen J, Devriese S, Camberlin C. First- and second-line bevacizumab in ovarian cancer: A Belgian cost-utility analysis. Cressman S, editor. PLoS One [Internet]. 2018 Apr 9 [cited 2019 Sep 30];13(4):e0195134. Available from: https://dx.plos.org/10.1371/journal.pone.0195134

170. Ball G, Xie F, Tarride J-E. Economic Evaluation of Bevacizumab for Treatment of Platinum-Resistant Recurrent Ovarian Cancer in Canada. PharmacoEconomics - Open [Internet]. 2018 Mar 29 [cited 2019 Sep 30];2(1):19–29. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29464667

171. Wysham WZ, Schaffer EM, Coles T, Roque DR, Wheeler SB, Kim KH. Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: A cost effectiveness analysis of the AURELIA trial. Gynecol Oncol [Internet]. 2017 May [cited 2019 Sep 30];145(2):340–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28291545

172. Duong M, Wright E, Martin-Nunez I, Yin L, Ghatage P, Fung-Kee-Fung M. The cost-effectiveness of bevacizumab for the treatment of advanced ovarian cancer in Canada. Curr Oncol [Internet]. 2016 Oct 26 [cited 2019 Sep 30];23(5):461. Available from: http://www.current-oncology.com/index.php/oncology/article/view/3139

173. Hinde S, Epstein D, Cook A, Embleton A, Perren T, Sculpher M. The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial. Value Heal [Internet]. 2016 Jun [cited 2019 Sep 30];19(4):431–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27325335

174. Chappell NP, Miller CR, Fielden AD, Barnett JC. Is FDA-Approved Bevacizumab Cost-Effective When Included in the Treatment of Platinum-Resistant Recurrent Ovarian Cancer? J Oncol Pract [Internet]. 2016 Jul [cited 2019 Sep 30];12(7):e775–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27246689

175. Cohn DE, Barnett JC, Wenzel L, Monk BJ, Burger RA, Straughn JM, et al. A cost–utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: Incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer. Gynecol Oncol [Internet]. 2015 Feb [cited 2019 Sep 30];136(2):293–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25449568

176. Chan JK, Herzog TJ, Hu L, Monk BJ, Kiet T, Blansit K, et al. Bevacizumab in Treatment of High-Risk Ovarian Cancer--A Cost-Effectiveness Analysis. Oncologist [Internet]. 2014 May 1 [cited 2019 Sep 30];19(5):523–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24721817

177. Mehta DA, Hay JW. Cost-effectiveness of adding bevacizumab to first line therapy for patients with

advanced ovarian cancer. Gynecol Oncol [Internet]. 2014 Mar [cited 2019 Sep 30];132(3):677–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24463160

178. Zhan M, Zheng H, Xu T, Yang Y, Li Q. Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial. Lung Cancer [Internet]. 2017 Aug [cited 2019 Sep 30];110:1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28676211

179. Reinhorn D, Sarfaty M, Leshno M, Moore A, Neiman V, Rosenbaum E, et al. A Cost-Effectiveness Analysis of Nivolumab and Ipilimumab Versus Sunitinib in First-Line Intermediate- to Poor-Risk Advanced Renal Cell Carcinoma. Oncologist [Internet]. 2019 Mar [cited 2019 Sep 30];24(3):366–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30710066

180. Wu B, Zhang Q, Sun J. Cost-effectiveness of nivolumab plus ipilimumab as first-line therapy in advanced renal-cell carcinoma. J Immunother Cancer [Internet]. 2018 Dec 20 [cited 2019 Sep 30];6(1):124. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30458884

181. Raphael J, Sun Z, Bjarnason GA, Helou J, Sander B, Naimark DM. Nivolumab in the Treatment of Metastatic Renal Cell Carcinoma. Am J Clin Oncol [Internet]. 2018 Dec [cited 2019 Sep 30];41(12):1235–42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29727313

182. Meng J, Lister J, Vataire A-L, Casciano R, Dinet J. Cost-effectiveness comparison of cabozantinib with everolimus, axitinib, and nivolumab in the treatment of advanced renal cell carcinoma following the failure of prior therapy in England. Clin Outcomes Res [Internet]. 2018 Apr [cited 2019 Sep 30];Volume 10:243–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29719414

183. Sarfaty M, Leshno M, Gordon N, Moore A, Neiman V, Rosenbaum E, et al. Cost Effectiveness of Nivolumab in Advanced Renal Cell Carcinoma. Eur Urol [Internet]. 2018 Apr [cited 2019 Sep 30];73(4):628–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28807351

184. Wan XM, Peng LB, Ma JA, Li YJ. Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and Chinese perspectives. Cancer [Internet]. 2017 Jul 15 [cited 2019 Sep 30];123(14):2634–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28301684

185. Petrou P. Looking for Her (2+): A systematic review of the economic evaluations of Trastuzumab in early stage HER 2 positive breast cancer. Expert Rev Pharmacoecon Outcomes Res [Internet]. 2019 Mar 4 [cited 2019 Sep 30];19(2):115–25. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30320510

186. Nixon NA, Hannouf MB, Verma S. A review of the value of human epidermal growth factor receptor 2 (HER2)-targeted therapies in breast cancer. Eur J Cancer [Internet]. 2018 Jan [cited 2019 Oct 12];89:72–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29241083

187. Verma V, Sprave T, Haque W, Simone CB, Chang JY, Welsh JW, et al. A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors. J Immunother Cancer [Internet]. 2018 Dec 23 [cited 2019 Oct 12];6(1):128. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30470252

188. Azar FE, Azami-Aghdash S, Pournaghi-Azar F, Mazdaki A, Rezapour A, Ebrahimi P, et al. Cost-effectiveness of lung cancer screening and treatment methods: a systematic review of systematic reviews.

BMC Health Serv Res [Internet]. 2017 Dec 19 [cited 2019 Sep 30];17(1):413. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28629461

189. Huxley N, Crathorne L, Varley-Campbell J, Tikhonova I, Snowsill T, Briscoe S, et al. The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation. Health Technol Assess (Rockv) [Internet]. 2017 Jun [cited 2019 Sep 30];21(38):1–294. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28682222

190. Park T, Choi C, Choi Y, Suh D-C. Cost-effectiveness of cetuximab for colorectal cancer. Expert Rev Pharmacoecon Outcomes Res [Internet]. 2016 Nov 20 [cited 2019 Sep 30];16(6):667–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27750444

191. Goldstein DA, Zeichner SB, Bartnik CM, Neustadter E, Flowers CR. Metastatic Colorectal Cancer: A Systematic Review of the Value of Current Therapies. Clin Colorectal Cancer [Internet]. 2016 Mar [cited 2019 Sep 30];15(1):1–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26541320

192. Saret CJ, Winn AN, Shah G, Parsons SK, Lin P-J, Cohen JT, et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. Blood [Internet]. 2015 Mar 19 [cited 2019 Oct 12];125(12):1866–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25655601

193. Poonawalla IB, Parikh RC, Du XL, VonVille HM, Lairson DR. Cost Effectiveness of Chemotherapeutic Agents and Targeted Biologics in Ovarian Cancer: A Systematic Review. Pharmacoeconomics [Internet]. 2015 Nov 14 [cited 2019 Oct 12];33(11):1155–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26072142

194. Diaby V, Tawk R, Sanogo V, Xiao H, Montero AJ. A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer. Breast Cancer Res Treat [Internet]. 2015 May 19 [cited 2019 Sep 30];151(1):27–40. Available from: http://link.springer.com/10.1007/s10549-015-3383-6

195. Lange A, Prenzler A, Frank M, Golpon H, Welte T, von der Schulenburg J-M. A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC). BMC Pulm Med [Internet]. 2014 Dec 4 [cited 2019 Oct 12];14(1):192. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25471553

196. Lange A, Prenzler A, Frank M, Kirstein M, Vogel A, von der Schulenburg JM. A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer. Eur J Cancer [Internet]. 2014 Jan [cited 2019 Oct 12];50(1):40–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24011538

197. Parkinson B, Pearson S-A, Viney R. Economic evaluations of trastuzumab in HER2-positive metastatic breast cancer: a systematic review and critique. Eur J Heal Econ [Internet]. 2014 Jan 24 [cited 2019 Oct 12];15(1):93–112. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23436142

198. Chouaïd C, Crequit P, Borget I, Vergnenegre A. Economic evaluation of first-line and maintenance treatments for advanced non-small cell lung cancer: A systematic review [Internet]. Vol. 7,

ClinicoEconomics and Outcomes Research. 2014 [cited 2019 Oct 12]. p. 9–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25548525

199. Geynisman DM, Chien C-R, Smieliauskas F, Shen C, Shih Y-CT. Economic evaluation of therapeutic cancer vaccines and immunotherapy: A systematic review. Hum Vaccin Immunother [Internet]. 2014 [cited 2019 Sep 30];10(11):3415–24. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25483656

7 ATTACHMENTS

7.1 Drug Master List

Active Substance	Product Name	Therapeutic Area	ATC Code	Marketing Authorisation Date	Condition / Indication
Atezolizumab	Tecentriq	Carcinoma, Transitional Cell, Carcinoma, Non-Small-Cell Lung	L01XC	20/09/2017	Advanced or metastatic Urothelial carcinoma and non-small cell lung cancer.
Avelumab	Bavencio	Neuroendocrine Tumors	L01XC31	17/09/2017	Metastatic Merkel cell carcinoma (MCC).
Axicabtagene ciloleucel	Yescarta	Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse	L01X	22/08/2018	Diffuse large B-cell lymphoma (DLBCL); Primary mediastinal large B-cell lymphoma (PMBCL).
Bevacizumab	Avastin	Carcinoma, Non-Small-Cell Lung, Breast Neoplasms, Ovarian Neoplasms, Colorectal Neoplasms, Carcinoma, Renal Cell	L01XC07	11/01/2005	Metastatic cancer of the colon or rectum, metastatic breast cancer,advanced non-small cell lung cancer, advanced or metastatic kidney cancer,epithelial cancer of the ovary, cancer of the fallopian tube or the peritoneum, recurrent or metastatic cancer of the cervix
Blinatumomab	Blincyto	Precursor Cell Lymphoblastic Leukemia-Lymphoma	L01XC	22/11/2015	B-precursor acute lymphoblastic leukaemia (ALL)
Brentuximab vedotin	Adcetris	Lymphoma, Non-Hodgkin, Hodgkin Disease	L01XC12	24/10/2012	CD30-positive Hodgkin's lymphoma
Cetuximab	Erbitux	Head and Neck Neoplasms, Colorectal Neoplasms	L01XC06	28/06/2004	Metastatic cancer of the colon or rectum, 'squamous-cell' cancers of the head and neck EGFR and RAS positive
Daratumumab	Darzalex	Multiple Myeloma	L01XC24	27/04/2017	Multiple Myeloma
Dinutuximab beta	Qarziba	Neuroblastoma	L01XC	8/05/2017	High-risk neuroblastoma
Durvalumab	Imfinzi	Carcinoma, Non-Small-Cell Lung	L01XC28	20/09/2018	Advanced PD-L1 positive Non-small cell lung cancer (NSCLC)
Elotuzumab	Empliciti	Multiple Myeloma	L01XC	10/05/2016	Multiple myeloma
Gemtuzumab ozogamicin	Mylotarg	Leukemia, Myeloid, Acute	L01XC05	18/04/2018	CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).
Ibritumomab tiuxetan	Zevalin	Lymphoma, Follicular	V10XX02	16/01/2004	Follicular B-cell non-Hodgkin's lymphoma in adults
Inotuzumab ozogamicin	Besponsa	Precursor Cell Lymphoblastic Leukemia-Lymphoma	L01XC	27/06/2017	CD-22 positive B-cell precursor acute lymphoblastic leukaemia (ALL)
Ipilimumab	Yervoy	Melanoma	L01XC11	11/07/2011	Adults and adolescents from 12 years of age with advanced melanoma and in adults with advanced renal cell carcinoma.
Necitumumab	Portrazza	Carcinoma, Non-Small-Cell Lung	L01	14/02/2016	Advanced squamous non-small cell lung cancer EGFR positive
Nivolumab	Opdivo	Melanoma, Hodgkin Disease, Carcinoma, Renal Cell, Carcinoma, Non-Small-Cell Lung	L01XC	18/06/2015	Melanoma, non-small cell lung cancer (NSCLC), advanced renal cell carcinoma,classical Hodgkin lymphoma, squamous cell cancer of the head and neck (SCCHN), urothelial cancer
Obinutuzumab	Gazyvaro	Leukemia, Lymphocytic, Chronic, B-Cell	L01XC15	21/07/2014	Previously untreated chronic lymphocytic leukaemia (CLL), follicular lymphoma (FL), another type of cancer of B-lymphocytes
Ofatumumab	Arzerra	Leukemia, Lymphocytic, Chronic, B-Cell	L01XC10	18/04/2010	Chronic lymphocytic leukaemia (CLL)
Olaratumab	Lartruvo	Sarcoma	L01XC27	9/11/2016	Advanced soft tissue sarcoma in adults
Panitumumab	Vectibix	Colorectal Neoplasms	L01XC08	2/12/2007	Wild-type RAS Metastatic colorectal cancer
Pembrolizumab	Keytruda	Melanoma, Hodgkin Disease, Carcinoma, Non-Small-Cell Lung	L01	15/07/2015	Advanced or metastatic: Melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin lymphoma,urothelial cancer, head and neck squamous cell carcinoma (HNSCC)
Pertuzumab	Perjeta	Breast Neoplasms	L01XC13	3/03/2013	HER2 Metastatic breast cancer, locally advanced, inflammatory or early-stage breast cancer
Ramucirumab	Cyramza	Stomach Neoplasms	L01XC	18/12/2014	Advanced gastric cancer or gastro-oesophageal junction adenocarcinoma, metastatic colorectal cancer, non-small cell lung cancer
Rituximab	MabThera	Lymphoma, Non-Hodgkin, Arthritis, Rheumatoid, Leukemia, Lymphocytic, Chronic, B-Cell	L01XC02	1/06/1998	Follicular lymphoma and diffuse large B cell non-Hodgkin's lymphoma ; Chronic Lymphocytic Leukaemia (CLL);
Talimogene laherparepvec	Imlygic	Melanoma	L01XX51	15/12/2015	Unresectable melanoma that is regionally or distantly metastatic with no bone, brain, lung or other internal organs metastases.
Tisagenlecleucel	Kymriah	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma, Lymphoma, Large B-Cell, Diffuse	L01	21/08/2018	B-cell acute lymphoblastic leukaemia (ALL), in children and young adults up to 25 years of age, Diffuse large B-cell lymphoma (DLBCL)
Trastuzumab	Herceptin	Stomach Neoplasms, Breast Neoplasms	L01XC03	27/08/2000	HER2 positive Early breast cancer, metastatic breast cancer; metastatic gastric cancer
Trastuzumab emtansine	Kadcyla	Breast Neoplasms	L01XC14	14/11/2013	Advanced or metastatic HER2 breast cancer

7.2 List of the Systematic Literature Reviews for cost-effectiveness studies on cancer imunnotherapies

Reference Number	Title of the Systematic Review	Publication Date	First Author
185	Looking for Her (2+): A systematic review of the economic evaluations of Trastuzumab in early stage HER 2 positive breast cancer.	April 2019	Petrou P
186	A review of the value of human epidermal growth factor receptor 2 (HER2)-targeted therapies in breast cancer.	January 2018	Nixon NA
187	A systematic review of the cost and cost-effectiveness studies of immune checkpoint inhibitors.	23 November 2018	Verma V
188	Cost-effectiveness of lung cancer screening and treatment methods: a systematic review of systematic reviews.	19 June 2017	Azar FE
189	The clinical effectiveness and cost-effectiveness of cetuximab (review of technology appraisal no. 176) and panitumumab (partial review of technology appraisal no. 240) for previously untreated metastatic colorectal cancer: a systematic review and economic evaluation.	June 2017	Huxley N
56	Multiple treatment comparison of seven new drugs for patients with advanced malignant melanoma: a systematic review and health economic decision model in a Norwegian setting.	21 August 2017	Pike E
190	Cost-effectiveness of cetuximab for colorectal cancer.	December 2016	Park T
191	Metastatic Colorectal Cancer: A Systematic Review of the Value of Current Therapies.	March 2016	Goldstein DA
192	Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses.	19 March 2015	Saret CJ
193	Cost Effectiveness of Chemotherapeutic Agents and Targeted Biologics in Ovarian Cancer: A Systematic Review.	November 2015	Poonawalla IB
194	A review of systematic reviews of the cost-effectiveness of hormone therapy, chemotherapy, and targeted therapy for breast cancer.	May 2015	Diaby V
57	Cost-effectiveness of therapies for melanoma.	April 2014	Johnston KM
195	A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC).	04 December 2014	Lange A
196	A systematic review of cost-effectiveness of monoclonal antibodies for metastatic colorectal cancer.	January 2014	Lange A
197	Economic evaluations of trastuzumab in HER2-positive metastatic breast cancer: a systematic review and critique.	January 2014	Parkinson B
198	Economic evaluation of first-line and maintenance treatments for advanced non-small cell lung cancer: a systematic review.	15 December 2014	Chouaïd C
199	Economic evaluation of therapeutic cancer vaccines and immunotherapy: a systematic review.	2014	Geynisman DM

7.3 **Bladder cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
58	Cost-effectiveness of Pembrolizumab in Second-line Advanced Bladder Cancer; Sarfaty M. et al; 2018; US, UK, CAN and AUS	**Target Population:** Second-line treatment of advanced bladder cancer **Intervention:** Pembrolizumab **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** 5 years **Cost type:** - **Discount Rates:** 3%/year (US,UK,AUS) and 1,5%/year (CAN) **Parameter Sources:** Clinical trials **WTP threshold:** (per QALY) US : $100 000-$150 000 UK: $25 000-$65 000 CAN: $16 000-$80 000 AUS: $32 000-$60 000 **Approach:** Markov Model	**Effect:** Pembrolizumab generated a gain of 0.36–0.37 QALYs compared with chemotherapy **Cost:** -	**ICER/ICUR:** US $122 557/QALY; UK: $91 995/QALY; CAN $90 099/QALY; and Australia $99 966/QALY **Main conclusion:** With standard WTP thresholds, pembrolizumab may be considered cost-effective in the US but not in the other countries examined.

7.4 **Brain cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
59	Economic Evaluation of Bevacizumab for the First-Line Treatment of Newly Diagnosed Glioblastoma Multiforme; Kovic B. Et al; Canada	**Target Population:** Patients newly diagnosed with glioblastoma multiforme (GBM) **Intervention:** Bevacizumab + SoC **Comparators:** SoC	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Databases and published studies **WTP threshold:** $100,000/QALY **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** increases of 0.13 quality-adjusted life-years **Cost:** $80,000 per patient over 2-year time horizon	**ICER/ICUR:** $607,966/QALY **Main conclusion:** Bevacizumab has only limited effectiveness and is therefore not likely to be cost effective in treating adult patients with newly diagnosed GBM.

7.5 **Breast cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
60	Cost-effectiveness of bevacizumab plus paclitaxel versus paclitaxel for the first-line treatment of HER2-negative metastatic breast cancer in specialist oncology centers in France; Petitjean A.; France; 2019	**Target Population:** First-line treatment of HER2-negative metastatic breast cancer **Intervention:** Bevacizumab + Paclitaxel **Comparators:** Paclitaxel	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database **WTP threshold:** €50,000/QALY and €80,000/QALY **Cost type:** Direct costs **Discount Rates:** 4%/year **Approach:** Markov Model	**Effect:** Incremental gain of 0.72 life years and 0.48 quality-adjusted life years **Cost:** Incremental lifetime cost of the addition of bevacizumab was €27,390, resulting in an incremental cost-effectiveness ratio	**ICER/ICUR:** €56,721/QALY and €66,874/QALY (triple negative patients) **Main conclusion:** Bevacizumab plus paclitaxel is likely to be cost-effective compared with paclitaxel alone for the first-line treatment of HER2-negative metastatic breast cancer
61	From Research to Policy Implementation: Trastuzumab in Early-Stage Breast Cancer Treatment in Thailand; Kongsakon R.; 2018; Thailand	**Target Population:** Patients with early-stage breast cancer who were considered human epidermal growth factor receptor 2/neu-positive **Intervention:** Trastuzumab + Paclitaxel **Comparators:** Paclitaxel	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies, expert panel and database **WTP threshold:** $3428/QALY **Cost type:** Direct costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The results revealed that the treatment cost and QALYs in the trastuzumab group yielded 4.59 QALYs. **Cost:** -	**ICER/ICUR:** $3387/QALY **Main conclusion:** A combination therapy that includes trastuzumab is a preferable choice and should be used in early-stage breast cancer treatment.
62	Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: A study of the Southeast Netherlands Breast Cancer Consortium; Seferina SC.; 2017; Netherlands	**Target Population:** Patients with stage I-III invasive breast cancer treated with curative intent **Intervention:** Trastuzumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials and published studies **WTP threshold:** €80,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 4%/year(C) and 1.5%/year(O) **Approach:** Markov Model	**Effect:** The incremental QALYs of the real world and the guideline scenarios were 0.827 and 0.861 respectively, while the incremental QALY of the trial scenario was 0.993. **Cost:** Costs were €243,216 and €239,657 for trastuzumab and no trastuzumab for the real world scenario, €224,443 and €218,948 for the guideline scenario	**ICER/ICUR:** €4,304/QALY (real-world); €6,382/QALY (guideline) and (trial) dominance **Main conclusion:** Adjuvant trastuzumab in the real world can be considered cost-effective
63	Cost-effectiveness of pertuzumab combined with trastuzumab and docetaxel as a first-line treatment for HER-2 positive metastatic breast cancer; Leung HWC.; 2018; Taiwan	**Target Population:** First-line treatment for HER-2 positive metastatic breast cancer **Intervention:** Pertuzumab + Trastuzumab + Docetaxel **Comparators:** Trastuzumab + Docetaxel	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Clinical trials, published studies and database **WTP threshold:** US$ 67,590/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Modeled median survival was 39.1 months for TD and 50.1 months for TDP **Cost:** -	**ICER/ICUR:** US$593,741 per QALY **Main conclusion:** Our model predicted that TDP would be cost-effective as a first-line treatment for HER-2 positive metastatic breast cancer, but only under favorable drug cost assumptions.
64	Economic evaluation of sequencing strategies in HER2-positive metastatic breast cancer in Mexico: a contrast between public and private payer perspective; Diaby V.; 2017; Mexico	**Target Population:** Patients with HER2-positive metastatic breast cancer **Intervention:** 1) 1st line: pertuzumab plus trastuzumab plus docetaxel [THP]; 2nd line: T-DM1; 3rd line: capecitabine plus lapatinib(THP → T-DM1 → Cape/Lapat). 2) (THP → Trastuz/Lapat → Trastuz/Cape) 3) (Trastuz/Docet → T-DM1 → Trastuz/Lapat) 4) (Trastuz/Docet → Trastuz/Lapat → Trastuz/Cape)	**Perspective:** Payer and Public **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials, published studies and database **WTP threshold:** $50,000/QALY, $100,000/QALY, $150,000/QALY, and $200,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Markov Model	**Effect:** Public payer perspective: The ranking of the non-dominated treatment sequences was as follows: Trastuz/Docet → Trastuz/Lapat → Trastuz/Cape followed by THP → T-DM1 → Cape/Lapat. Private payer perspective: The ranking of the non-dominated treatment sequences, was as follows: Trastuz/Docet → T-DM1 → Trastuz/Lapat followed by Trastuz/Docet → Trastuz/Lapat → Trastuz/Cape, and THP → T-DM1 → Cape/Lapat. **Cost:** -	**ICER/ICUR:** - **Main conclusion:** In Mexico, the use of at least three lines of trastuzumab in combination with other therapies, but not with pertuzumab or TDM-1, represents the most cost-effective option for patients covered by the public healthcare system, and this sequence should be made available for all patients.

7.6 **Breast cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
65	Adjuvant Trastuzumab Therapy for Early HER2-Positive Breast Cancer in Iran: A Cost-Effectiveness and Scenario Analysis for an Optimal Treatment Strategy; Ansaripour A.; 2018; Iran	**Target Population:** Early HER2-positive breast cancer **Intervention:** (12 months trastuzumab, 9 months , 6 months) + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** €21,000/QALY and €28,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model	**Effect:** Incremental quality-adjusted life-years (QALYs) were 0.65 (6 months), 0.87 (9 months) and 1.14 (12 months) **Cost:** Incremental costs (versus no trastuzumab) were €8826 (6 months), €13,808 (9 months) and €18,588 (12 months)	**ICER/ICUR:** €16,695/QALY (12 months) , €16,370/QALY (9 months) and €14,625/QALY (6 months) **Main conclusion:** 6 months of trastuzumab may be the most cost-effective option for Iran. The lower absolute WTP threshold and lower life expectancy compared with high-income countries are two crucial parameters in the cost effectiveness of interventions in MICs. It is therefore necessary to strike a balance between maximum population health and maintaining affordability in these countries.
66	Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective; Clarke CS.; 2017; England	**Target Population:** Early HER2-positive breast cancer **Intervention:** 9 week adjuvant trastuzumab and 12 month adjuvant trastuzumab **Comparators:** No adjuvant trastuzumab	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** £30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model and Decision Tree Model	**Effect:** The 9-week regimen results in 0.8 more QALYs per patient than the 12-month **Cost:** The 9-week regimen results in a cost saving of £23,197 per patient compared with the 12-month regimen	**ICER/ICUR:** £33,000/QALY (12 months) and 9 weeks dominates **Main conclusion:** Our CEA results suggest that 9-week trastuzumab dominates 12-month trastuzumab in cost-effectiveness terms at conventional thresholds of willingness to pay for a QALY, and the 9-week regimen is also suggested to be as clinically effective as the 12-month regimen according to the NMA and Bucher analyses.
67	Real-world and trial-based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients: a study of the Southeast Netherlands Breast Cancer Consortium; van Kampen RJW.; 2017; Netherlands	**Target Population:** HER2-negative metastatic breast cancer **Intervention:** Bevacizumab + Taxane **Comparators:** Taxane monotherapy	**Perspective:** Payer **Time Horizon:** Lifetime Parameter Sources: Published studies and clinical trials **WTP threshold:** €80,000/QALY **Cost type:** - **Discount Rates:** 4%/year (C) and 1,5%/year (O) **Approach:** State Trasition Model	**Effect:** In both the real-world and trial scenarios, bevacizumab-taxane is and more effective (incremental QALYs of 0.362 and 0.189, respectively **Cost:** In both the real-world and trial scenarios is more expensive (incremental costs of €56,213 and €52,750, respectively)	**ICER/ICUR:** €155,261/QALY (real world scenario) and €278,711/QALY (trial scenario) **Main conclusion:** According to the Dutch informal threshold, bevacizumab in addition to taxane treatment was not considered cost-effective for HER2-negative metastatic breast cancer both in a real-world and in a trial scenario.
68	Cost-effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States; Diaby V.; 2016; United States	**Target Population:** HER2-positive metastatic breast cancer **Intervention:** 1) 1st line: pertuzumab plus trastuzumab plus docetaxel (THP); 2nd line: T-DM1; 3rd line: capecitabine plus lapatinib(THP → T-DM1 → Cape/Lapat).	2) (THP → Trastuz/Lapat → Trastuz/Capel 3) (Trastuz/Docet → T-DM1 → Trastuz/Lapat) 4) (Trastuz/Docet → Trastuz/Lapat → Trastuz/Cape) **Comparators:** Against each others	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and trials **WTP threshold:** $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model	**Effect:** The combination of trastuzumab, pertuzumab, and docetaxel (THP) as first-line therapy, trastuzumab emtansine (T-DM1) as second-line therapy, and lapatinib/capecitabine third-line resulted in 1.81 QALYs. The combination of trastuzumab/docetaxel as first line without subsequent T-DM1 or pertuzumab yielded 1.41 QALYs. The least clinically effective sequence (1.27 QALYs) was trastuzumab/docetaxel as first-line therapy, T-DM1 as second-line therapy, and trastuzumab/lapatinib as third-line therapy. **Cost:** The combination of trastuzumab, pertuzumab, and docetaxel (THP) as first-line therapy, trastuzumab emtansine (T-DM1) as second-line therapy, and lapatinib/capecitabine third-line had a cost of $335,231.35. The combination of trastuzumab/docetaxel as first line without subsequent T-DM1 or pertuzumab came at a cost of $175,240.69. The least clinically effective sequence, but most cost-effective at a total cost of $149,250.19, was trastuzumab/docetaxel as first-line therapy, T-DM1 as second-line therapy, and trastuzumab/lapatinib as third-line therapy.	**ICER/ICUR:** - **Main conclusion:** Our results suggest that THP as first-line therapy, followed by T-DM1 as second-line therapy, would require at least a 50 % reduction in the total drug acquisition cost for it to be considered a cost-effective strategy.

7.7 **Breast cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
69	Cost-effectiveness analysis of trastuzumab emtansine (T-DM1) in human epidermal growth factor receptor 2 (HER2); positive advanced breast cancer.; Le QA; 2016; United States	**Target Population:** HER2-positive advanced breast cancer (ABC) previously treated with trastuzumab and a taxane **Intervention:** trastuzumab emtansine (T-DM1) **Comparators:** lapatinib plus capecitabine (LC), monotherapy with capecitabine (C)	**Perspective:** Payer and Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct and indirect costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The EMILIA clinical trial demonstrated that T-DM1 significantly increased the median progression-free survival (PFS) to 3.2 months (P\0.001) and overall survival (OS) to 5.8 months (P\0.001) relative to combination therapy with lapatinibpluscapecitabine(LC)inpatientswithHER2positive advanced breast cancer (ABC) previously treated with trastuzumab and taxane **Cost:** -	**ICER/ICUR:** T-DM1 to LC and T-DM1 to C were $183,828/QALY and $126,001/QALY respectively (societal perspective)and $220,385/QALY (T-DM1 vs. LC) and $168,355/QALY (T-DM1 vs. C) from payer perspective **Main conclusion:** From both perspectives of the US payer and society, T-DM1 is not cost-effective when comparing to the LC combination therapy at a willingness-to-pay threshold of $150,000/QALY. T-DM1 might have a better chance to be cost-effective compared to capecitabine monotherapy from the US societal perspective.
70	Adjuvant Trastuzumab in HER2-Positive Early Breast Cancer by Age and Hormone Receptor Status: A Cost-Utility Analysis.; Leung W; 2016; New Zealand	**Target Population:** Node-positive HER2+ early breast cancer **Intervention:** Trastuzumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and clinical trials **WTP threshold:** US$30,300; £23,700; £21,200 **Cost type:** - **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Incremental quality-adjusted life-years for trastuzumab versus chemotherapy alone are two times higher (2.33 times for the age group 50-54 y; 95% CI 2.29-2.37) for the worst prognosis (ER-/PR-) subtype compared to the best prognosis (ER+/PR+) subtype **Cost:** Trastuzumab (2011 PPP-adjusted US$45,400/€35,900/£21,900 for 1 year at formulary prices)	**ICER/ICUR:** - **Main conclusion:** This study highlights how cost-effectiveness can vary greatly by heterogeneity in age and hormone receptor subtype. Resource allocation and licensing of subsidised therapies such as trastuzumab should consider demographic and clinical heterogeneity; there is currently a profound disconnect between how funding decisions are made (largely agnostic to heterogeneity) and the principles of personalised medicine.
71	The real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu-positive early breast cancer in Taiwan.; Lang HC; 2016; Taiwan	**Target Population:** HER-2/neu-positive early breast cancer **Intervention:** 1 year trastuzumab adjuvant therapy **Comparators:** No adjuvant therapy	**Perspective:** Payer **Time Horizon:** 20 years Parameter Sources: Published studies and databases **WTP threshold:** US$67,065/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The model showed that adjuvant trastuzumab treatment in HER-2/neu positive early breast cancer yielded 1.631 quality-adjusted life-years (QALY) compared with no trastuzumab treatment **Cost:** -	**ICER/ICUR:** $51,863/QALY **Main conclusion:** From this real-world study, 1-year adjuvant trastuzumab treatment is likely to be a cost-effective therapy for patients with HER-2 positive breast cancer at the willingness-to-pay threshold of 3-times GDP per capita in Taiwan.

7.8 **Breast cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
72	A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada.; Beauchemin C.; 2016; Canada	**Target Population:** Metastatic Breast Cancer **Intervention:** Lapatinib + Letrozole **Comparators:** Letrozole alone, Trastuzumab + Anastrozole and Anastrozole alone	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** **WTP threshold:** CA$100 000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** Incremental QALY's against letrozole alone, trastuzumab plus anastrozole, and anastrozole alone are 0,38 ; 0,21 and 0,49, respectively. **Cost:** Incremental cost against letrozole alone, trastuzumab plus anastrozole, and anastrozole alone are CA$49,559 , CA$11,643 and CA$49,736, respectively.	**ICER/CUR:** Lapatinib plus letrozole compared with letrozole alone, trastuzumab plus anastrozole, and anastrozole alone are, thus, estimated at CA$131 811/QALY, CA$56 211/QALY, and CA$102 477/QALY, respectively. **Main conclusion:** In conclusion, the GPMBC model can be very valuable for quickly generating valid and reliable cost-utility analyses of new treatments for MBC in a Canadian context. Such a global model would be useful for decision-making purposes because it standardizes the parameters used to estimate the incremental cost per QALY of new treatments for MBC, thus allowing the comparison of the results of economic evaluations in MBC on the same basis. When fully validated, the GPMBC model could be used as a benchmark for drug reimbursement authorities in Canada, and possibly in other countries, despite contextual
73	Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer.; Durkee BY; 2016; United States	**Target Population:** Patients with human epidermal growth factor receptor 2 (HER2) -overexpressing metastatic breast cancer **Intervention:** Pertuzumab and Docetaxel + Trastuzumab **Comparators:** Docetaxel + Trastuzumab	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Modeled median survival was 39.4 months for TH and 56.9 months for THP. The addition of pertuzumab resulted in an additional 1.81 life-years gained, or 0.62 QALYs. **Cost:** -	**ICER/ICUR:** $472,668/QALY **Main conclusion:** THP in patients with metastatic HER2-positive breast cancer is unlikely to be cost effective in the United States.
74	Everolimus plus exemestane versus bevacizumab-based chemotherapy for second-line treatment of hormone receptor-positive metastatic breast cancer in Greece: An economic evaluation study.; Kourlaba G.; 2015; Greece	**Target Population:** Postmenopausal women with HR+/HER2- advanced breast cancer (BC) **Intervention:** Everolimus plus exemestane **Comparators:** Bevacizumab-based chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** €36,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model	**Effect:** The discounted quality-adjusted survival of patients treated with EVE plus EXE was greater by 0.035 and 0.004 QALYs, compared to BEV plus PACL and BEV plus CAPE, respectively **Cost:** The total lifetime cost per patient was estimated at £55,022, €67,980, and €62,822 for EVE plus EXE, BEV plus PACL, and BEV plus CAPE, respectively	**ICER/ICUR:** According to the base case results, EVE plus EXE dominates both active comparators, as it is associated with lower costs and higher clinical efficacy in both cases. **Main conclusion:** Our results suggest that EVE plus EXE may be a dominant alternative relative to BEV plus PACL and BEV plus CAPE for the treatment of HR+/HER2-advanced BC patients failing initial therapy with NSAIs.
75	Cost-effectiveness analysis of trastuzumab in the adjuvant treatment for early breast cancer.; Aboutorabi A.; 2014; Iran	**Target Population:** Women with HER2 positive early breast cancer **Intervention:** 1 year adjuvant trastuzumab therapy **Comparators:** AC-T regimen	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Clinical trials and published studies **WTP threshold:** $10,000-$15,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Therefore, the new intervention produced an extra 0.87 QALYs **Cost:** The total costs for AC-T and AC-T adjuant treatments were 12,388 USD and 56,984 USD, respectively.	**ICER/ICUR:** US$ 51,302/QALY **Main conclusion:** By using threshold of 3 times GDP per capita, as per World Health Organization (WHO) recommendation, 12 months trastuzumab adjuvant chemotherapy is not a cost-effective therapy for patients with HER2-positive breast cancer in Iran.

7.9 **Breast cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
76	ErbB2+ metastatic breast cancer treatment after progression on trastuzumab: a cost-effectiveness analysis for a developing country.; Chicaiza-Becerra L.; 2014; Colombia	**Target Population:** ErbB2+MBC patients who progressed after a first scheme involving trastuzumab **Intervention:** Lapatinib + Capecitabine **Comparators:** Trastuzumab + chemotherapy agent (capecitabine, vinorelbine or a taxane)	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Published studies, clinical trials and database **WTP threshold:** three times COP $11,216,656 **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Incremental effectiness considered was - 0.018 for every one of the comparators. **Cost:** Incremental costs considered were the following, COP $111,679,005 (T+C); COP $100,284,893 (T+P); COP $104,594,593 (T+D) and COP $105,313,611 (T+V)	**ICER/ICUR:** L+C was the most effective and least expensive alternative. L+C cost-effectiveness ratio was COP $49,725,045 per progression-free year (average Colombian exchange rate in 2009 was COP $2,156 per dollar). **Main conclusion:** Lapatinib was cost-effective compared to its alternatives for treating MBC after progression on trastuzumab using a Colombian decision analytic model.
77	Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada.; Attard CL.; 2015; Canada	**Target Population:** Neoadjuvant locally advanced, inflammatory, or early HER2-positive breast cancer **Intervention:** Pertuzumab, Trastuzumab and Docetaxel **Comparators:** Trastuzumab + Docetaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Plubished studies and clinical trials **WTP threshold:** CAD$100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** Incremental LYs and QALYs in both analyses were 0,333 and 0,310, respectively. **Cost:** The incremental cost were CAD$7879 in the NeoSphere analysis and CAD$14,337 in the TRYPHAENA analysis.	**ICER/ICUR:** CAD$25,388/QALY (NeoSphere analysis) to $46,196/QALY (TRYPHAENA analysis) **Main conclusion:** Given the improvement in clinical efficacy and a favorable cost per QALY, the addition of pertuzumab in the neoadjuvant setting represents an attractive treatment option for HER2-positive eBC patients.
78	Modelling the cost-effectiveness of adjuvant lapatinib for early-stage breast cancer.; Candon D.; 2014; Ireland	**Target Population:** Early-stage breast cancer **Intervention:** Trastuzumab + Lapatinib + Carboplatin + Docetaxel **Comparators:** Trastuzumab + Carboplatin + Docetaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials and database **WTP threshold:** €45,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 4%/year **Approach:** Markov Model	**Effect:** Since no efficacy data are available for combining adjuvant lapatinib with trastuzumab, we ran the model assuming five different hypothetical hazard ratios for disease free survival when lapatinib is added to TCH (TCH was used as the control group). The hazard ratios were 0.9, 0.8, 0.7, 0.6, and 0.5 **Cost:** Incremental cost varied between €9,855.66 and €8,768.58	**ICER/ICUR:** Depending on different hazard ratios are €53 089/QALY, €27 893/QALY, €18 463/QALY, €13 527/QALY and €10 490/QALY. **Main conclusion:** Adjuvant lapatinib regimen would be considered cost-effective for patients with HER2-positive early-stage breast cancer for four of the five hypothesised hazard ratios. Data from both adjuvant and neoadjuvant trials suggest that the hazard ratio required to achieve cost-effectiveness for adjuvant lapatinib is both possible and plausible.
79	Markov model and cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer.; Refaat T.; 2014; United States	**Target Population:** HER2-negative metastatic breast cancer **Intervention:** Bevacizumab + Paclitaxel **Comparators:** Paclitaxel	**Perspective:** Payer and Patient **Time Horizon:** 5 years **Parameter Sources:** Database and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Markov Model and Decision Tree Model	**Effect:** Marginal efficacy of 0.369 QALYs **Cost:** The marginal cost between paclitaxel alone versus bevacizumab and paclitaxel was $86,000	**ICER/ICUR:** $232,720.72/QALY **Main conclusion:** This study demonstrates that, despite a significant progression-free survival advantage, the addition of bevacizumab to paclitaxel is not cost effective for the cohort of patients with HER2-negative MBC included in our analysis

7.10 **Cervical cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
80	Is the routine use of bevacizumab in the treatment of women with advanced or recurrent cancer of the cervix sustainable?; Klag N.; 2016; United States	**Target Population:** Women with advanced, recurrent or persistent squamous cell carcinoma of the cervix **Intervention:** CP with bevacizumab (CP+B); paclitaxel/topotecan (PT); PT with bevacizumab (PT+B) **Comparators:** cisplatin/paclitaxel (CP)	**Perspective:** - **Time Horizon:** - **Parameter Sources:** Published studies, literature and clinical trials **WTP threshold:** $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Decision Analytical Model	**Effect:** The mean survival in years by intervention were 1.1 for CP, 1.35 for CP+B, 1.25 for PT and 1,56 for PT+B **Cost:** The mean total cost by intervention was $32,966 for CP, $96,842 for CP+B, 71,620 for PT and 109,211 for PT+B	**ICER/ICUR:** $133,559/QALY (CP + B), $511,947/QALY (PT), $124,576/QALY (PT+B) **Main conclusion:** CP is the most cost effective regimen. A 12-month increase in overall survival will not even make the newer combinations cost effective. The use of bevacizumab is not sustainable at today's costs.
81	A Markov model to evaluate cost-effectiveness of antiangiogenesis therapy using bevacizumab in advanced cervical cancer.; Minion LE.; 2015; United States	**Target Population:** Recurrent/persistent and metastatic cervical cancer **Intervention:** Bevacizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Database and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Markov Model	**Effect:** The use of Bevacizumab with chemotherapy resulted in 3.5 months of life gained **Cost:** The estimated total cost of therapy with bevacizumab is approximately 13.2 times that for chemotherapy alone, adding $73,791	**ICER/ICUR:** $295,164/QALY **Main conclusion:** Increased costs are primarily related to the cost of drug and not the management of bevacizumab-induced complications. Cost reductions in bevacizumab result in dramatic declines in the ICER, suggesting that cost reconciliation in advanced cervical cancer may be possible through the availability of biosimilars, and/or less expensive, equally efficacious anti-angiogenesis agents.
82	Bevacizumab in recurrent, persistent, or advanced stage carcinoma of the cervix: is it cost-effective?; Phippen NT.; 2015; United States	**Target Population:** Recurrent, persistent, or advanced stage carcinoma of the cervix **Intervention:** Bevacizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** Database and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Decision Analytical Model	**Effect:** A 3.7 month OS advantage with Chemo + Bev arm **Cost:** The cost of Chemo + Bev was $53,784 compared to $5,688 for the Chemo arm.	**ICER/ICUR:** $155,000/QALY **Main conclusion:** With an ICER of $155,000/QALY, the addition of bevacizumab to standard chemotherapy approaches common cost-effectiveness standards. Moderately discounting the cost of bevacizumab or using a smaller dose significantly alters its affordability.

7.11 **Colorectal cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
83	Cost-effectiveness of Maintenance Capecitabine and Bevacizumab for Metastatic Colorectal Cancer.; Sherman SK.; 2018; United States	**Target Population:** Patients with unresectable metastatic colorectal cancer who had stable disease or better following induction chemotherapy; **Intervention:** Bevacizumab + Capecitabine **Comparators:** Observation	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Databases and Clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 4%/year (C) and 1.5%/year (O) **Approach:** Markov Model	**Effect:** Mean QALYs accrued were 1.34 for maintenance therapy and 1.20 for observation. **Cost:** After 29 model iterations corresponding to 60 months of follow-up, mean per-patient costs were $105 239 for maintenance therapy and $21.10 for observation.	**ICER/ICUR:** $725,601/QALY **Main conclusion:** Antineoplastic therapy is expensive for payers and society. The price of capecitabine and bevacizumab maintenance therapy would need to be reduced by 93% to make it cost-effective, a finding useful for policy decision making and payment negotiations.
84	Impact of drug substitution on cost of care: an example of economic analysis of cetuximab versus panitumumab.; Xu Y.; 2018; United States	**Target Population:** Chemo-refractory metastatic CRC (mCRC) with wild-type KRAS **Intervention:** Panitumumab **Comparators:** Cetuximab	**Perspective:** Societal **Time Horizon:** 2 years **Parameter Sources:** Published studies, databases and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct and indirect costs **Discount Rates:** - **Approach:** Markov Model	**Effect:** Both panitumumab and cetuximab produced 0.45 QALYs **Cost:** At a cost per patient of $66,006 panitumumab and $71,956 for cetuximab	**ICER/ICUR:** $728,036 per QALY **Main conclusion:** Panitumumab can lower the cost of care without impacting outcomes in chemo-refractory mCRC settings. This finding provides a strong argument to consider panitumumab in lieu of cetuximab in these patients.
85	Cost-effectiveness of immune checkpoint inhibitors for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer.; Chu JN.; 2019; United States	**Target Population:** Patients with MSI-H/dMMR mCRC **Intervention:** Ipilimumab and nivolumab **Comparators:** Nivolumab, trifluridine and tipiracil (third-line treatment), and mFOLFOX6 and cetuximab (first-line treatment)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Databases, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical Model	**Effect:** Ipilimumab with nivolumab was the most effective strategy (10.69 life-years and 9.25 QALYs for the third line; 10.69 life-years and 9.44 QALYs for the first line) in comparison with nivolumab (8.21 life-years and 6.76 QALYs for the third line; 8.21 life-years and 7.00 QALYs for the first line), trifluridine and tipiracil (0.74 life-years and 0.07 QALYs), and mFOLFOX6 and cetuximab (2.72 life-years and 1.63 QALYs). **Cost:** -	**ICER/ICUR:** However, neither checkpoint inhibitor therapy was cost-effective in comparison with trifluridine and tipiracil (nivolumab ICER, $153,000; ipilimumab and nivolumab ICER, $162,700) or mFOLFOX6 and cetuximab (nivolumab ICER, $150,700; ipilimumab and nivolumab ICER, $158,700). **Main conclusion:** This modeling analysis found that both single and dual checkpoint blockade could be significantly more effective for MSI-H/dMMR mCRC than chemotherapy, but they were not cost-effective, largely because of drug costs. Decreases in drug pricing and/or the duration of maintenance nivolumab could make ipilimumab and nivolumab cost-effective. Prospective clinical trials should be performed to explore the optimal duration of maintenance nivolumab
86	A within-trial cost-effectiveness analysis of panitumumab compared with bevacizumab in the first-line treatment of patients with wild-type RAS metastatic colorectal cancer in the US.; Graham CN.; 2018; United States	**Target Population:** First-line treatment of patients with wild-type RAS metastatic colorectal cancer (mCRC), **Intervention:** Panitumumab + mFOLFOX6 **Comparators:** Bevacizumab + mFOLFOX6	**Perspective:** Payer Time Horizon: Lifetime **Parameter Sources:** Databases and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** Compared with bevacizumab, the use of panitumumab resulted in an incremental quality-adjusted life-year (QALY) of 0.445 **Cost:** Compared with bevacizumab, the use of panitumumab resulted in an incremental cost of US $60,286,	**ICER/ICUR:** $135,391/QALY **Main conclusion:** The efficacy of panitumumab in extending progression-free and overall survival and improving quality of life makes it a cost-effective option for first-line treatment of patients with wild-type RAS mCRC compared with bevacizumab.
87	Real-world cost-effectiveness of cetuximab in the third-line treatment of metastatic colorectal cancer based on patient chart review in the Netherlands; Uyl-de Groot CA; 2018; Netherlands	**Target Population:** Third-line treatment of patients with KRAS wild-type (wt) metastatic colorectal cancer (mCRC) **Intervention:** Cetuximab **Comparators:** Best Supportive Care	**Perspective:** - **Time Horizon:** 4 years **Parameter Sources:** Real world studies, Clinical trials and databases **WTP threshold:** €100,000-€150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 4%/year (C) and 1,5%/year (O) **Approach:** Markov Model	**Effect:** Administration of cetuximab in third-line treatment of mCRC resulted in a gain of 0.29 LYs and 0.25 QALYs compared with BSC. In the four-year study period **Cost:** Average discounted healthcare costs were €36,637 in the cetuximab group vs. €3648 in the BSC group.	**ICER/ICUR:** In the real-world setting were €114,907and €133,527 per LY and QALY gained, respectively. **Main conclusion:** Results of this cost-effectiveness analysis showed that third-line treatment with cetuximab for patients with KRAS (exon 2) wt mCRC offered clinical benefits at additional cost. The real-world ICERs were in line with those of previously published cetuximab and panitumumab cost-utility models

7.12 **Colorectal cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
88	Economic Analysis of First-Line Treatment with Cetuximab or Panitumumab for RAS Wild-Type Metastatic Colorectal Cancer in England; Tikhonova IA; 2018; England	**Target Population:** Patients with previously untreated RAS wild-type (i.e. non-mutated) metastatic colorectal cancer, not eligible for liver resection at baseline **Intervention:** Cetuximab + Panitumumab + FOLFOX or FOLFIRI **Comparators:** FOLFOX or FOLFIRI	**Perspective:** Payer and Patient **Time Horizon:** Lifetime **Parameter Sources:** Published studies **WTP threshold:** £50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Partitioned Survival Model	**Effect:** The incremental QALYs for the different therapies considered in the study were the following: 0.49 QALYs for CET + FOLFIRI vs. FOLFIRI; 0.12 QALYs for CET + FOLFOX vs. FOLFOX and 0.31 QALYs for PAN+ FOLFOX VS FOLFOX **Cost:** The incremental costs for the different therapies considered in the study were the following: $40,947 for CET + FOLFIRI vs. FOLFIRI; 29,706 for CET + FOLFOX vs. FOLFOX and $32,797 for PAN+ FOLFOX VS FOLFOX	**ICER/ICUR:** £83,168/QALY for CET + FOLFIRI vs. FOLFIRI and ICER =£243,975/QALY for CET + FOLFOX vs. FOLFOX and ICER = £106,276 (PAN+ FOLFOX VS FOLFOX) **Main conclusion:** Cetuximab and panitumumab were recommended by the National Institute for Health and Care Excellence for patients with previously untreated RAS wild-type metastatic colorectal cancer, not eligible for liver resection at baseline, for use within the National Health Service in England.
89	RAS testing and cetuximab treatment for metastatic colorectal cancer: a cost-effectiveness analysis in a setting with limited health resources; Wu B.; 2017; China	**Target Population:** First-line treatment in patients with metastatic colorectal cancer (mCRC) **Intervention: cetuximab + FOLFIRI chemotherapy** **Comparators: FOLFIRI chemotherapy**	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Literature, Published studies and clinical trials **WTP threshold:** $22,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** For patients with advanced mCRC, the cetuximab regimen yielded an increase of 0.149 progression-free life-years (LYs), 0.73 overall LYs, or 0.63 quality-adjusted life-years (QALYs) in comparison with the chemotherapy regimen. **Cost:** The incremental direct medical cost amounted to $8,843 and $17,086 with and without a patient assistance program (PAP) over the 10-year period, respectively.	**ICER/ICUR:** $27,145/QALY and (w/ PAP) $14,049/QALY **Main conclusion:** RAS testing with cetuximab treatment is likely to be cost-effective for patients with mCRC when PAP is available in China.
90	Cost-effectiveness analysis of XELOX versus XELOX plus bevacizumab for metastatic colorectal cancer in a public hospital school.; Ungari AQ.; 2017; Brazil	**Target Population:** Metastatic colorectal cancer in first-line therapy **Intervention:** Bevacizumab + XELOX **Comparators:** XELOX	**Perspective:** - **Time Horizon:** 5 years **Parameter Sources:** Published studies, databases and clinical trials **WTP threshold:** 81,687BRL **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model and Decision Tree Model	**Effect:** The analysis of the model proposed resulted in an incremental difference of 2.25 Months Life Gained **Cost:** The analysis of the model proposed resulted in an incremental cost difference of 47,833.57BRL	**ICER/ICUR:** 21,231.43 BRL per month of life gained **Main conclusion:** Although the XELOX plus bevacizumab regimen is a more expensive and more effective treatment than XELOX, it does not fit the reimbursement values fixed by the public healthcare system in Brazil.
91	Bevacizumab for Metastatic Colorectal Cancer: A Global Cost-Effectiveness Analysis.; Goldstein DA.; 2017; US, UK, CAN, AUS and Israel	**Target Population:** First-line chemotherapy in metastatic colorectal cancer (mCRC) **Intervention:** Bevacizumab + SoC **Comparators:** SoC	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** $150,000/QALY **Cost type:** Direct medical cost **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The number of life years (LYs) and QALYs was unchanged from those reported in the previous U.S.-based study and identical in each country: the addition of bevacizumab to FOLFOX provided an additional benefit of 0.14 LYs or 0.10 QALYs **Cost:** In the U.S., U.K., Canada, Australia, and Israel, in comparison with the base case results, that addition of bevacizumab to FOLFOX resulted in an additional cost of $571,166, $352,734, $350,536, $277,441, and $357,888 per QALY gained, respectively.	**ICER/ICUR:** ICER was in the U.S. ($571,000/QALY) and the lowest was in Australia ($277,000/QALY). In Canada, the U.K., and Israel, ICERs ranged between $351,000 and $358,000 per QALY **Main conclusion:** The cost-effectiveness of bevacizumab varies significantly between multiple countries. By conventional thresholds, bevacizumab is not cost-effective in metastatic colon cancer in the U.S., the U.K., Australia, Canada, and Israel.
92	Cost-effectiveness of cetuximab and panitumumab for chemotherapy-refractory metastatic colorectal cancer; Carvalho AC.; 2017; Brazil	**Target Population:** RAS wild type metastatic colorectal cancer after chemotherapy failure **Intervention:** Cetuximab alone and Panitumumab alone **Comparators:** Best supportive care	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $24,751/LY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** The incorporation of cetuximab or panitumumab resulted in 0.22 LY (2.64 months) incremental survival over BSC **Cost:** Treatment with BSC generated an average cost of $429.13, while a patient undergoing treatment with panitumumab or cetuximab cost $11,859.04 and $13,043.32, respectively	**ICER/ICUR:** $52,772/LY (panitumumab) and $58,240/LY (cetuximab) **Main conclusion:** Our economic evaluation demonstrates that both cetuximab and panitumumab are not a cost-effective approach in RAS-wt mCRC patients. Discussion about drug price should be prioritized to enable incorporation of these monoclonal antibodies in the SUS.

7.13 **Colorectal cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
93	Cost-effectiveness of capecitabine and bevacizumab maintenance treatment after first-line induction treatment in metastatic colorectal cancer.; Franken MD.; 2017; Netherlands	**Target Population:** Maintenance treatment after first-line induction treatment in metastatic colorectal cancer **Intervention:** Bevacizumab + capecitabine **Comparators:** Observation	**Perspective:** - **Time Horizon:** - **Parameter Sources:** Database, Published studies and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 4%/year (C) and 1,5%/year (O) **Approach:** Decision Analytical Model	**Effect:** CAP-B maintenance compared with observation resulted in 0.21 QALYs (0.18LYs) **Cost:** CAP-B maintenance compared with observation resulted in a mean cost increase of €36,845	**ICER/ICUR:** For patients achieving complete or partial response on capecitabine, oxaliplatin, bevacizumab induction treatment, an ICER of €149,300 per QALY and ICER of €175,452 per QALY, respectively. **Main conclusion:** CAP-B maintenance results in improved health outcomes measured in QALYs and LYs compared with observation, but also in a relevant increase in costs. Despite the fact that there is no consensus on cost-effectiveness thresholds in cancer treatment, CAP-B maintenance may not be considered cost-effective.
94	Cost-effectiveness analysis in the Spanish setting of the PEAK trial of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer.; Rivera F.; 2017; Spain	**Target Population:** Patients with wild-type RAS metastatic colorectal cancer (mCRC) **Intervention:** Panitumumab + mFOLFOX6 **Comparators:** Bevacizumab + mFOLFOX6	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials and published studies **WTP threshold:** €30,000/QALY **Cost type:** Direct costs **Discount Rates:** 3%/year **Approach:** Semi-Markov Model	**Effect:** Panitumumab and FOLFOX6 resulted in more LYG vs bevacizumab and FOLFOX6: 3.685 and 2.796 and a QALY gain of 2.753 and 2.107, respectively. **Cost:** Treatment with panitumumab had a higher overall cost than with bevacizumab: e72,203 and e57,485, respectively.	**ICER/ICUR:** €22,794/QALY and €16,567/LY **Main conclusion:** Based on the PEAK Phase II clinical trial and taking into account Spanish costs, the results of the analysis showed that first-line treatment of mCRC with panitumumab + mFOLFOX6 could be considered a cost-effective option compared with bevacizumab + mFOLFOX6 for the Spanish NHS.
95	Cost-Effectiveness of Treatment Sequences of Chemotherapies and Targeted Biologics for Elderly Metastatic Colorectal Cancer Patients.; Parikh RC.; 2017; United States	**Target Population:** mCRC patients aged 65 years and older **Intervention:** first-line oxaliplatin/irinotecan followed by second-line oxaliplatin/irinotecan + bevacizumab (OI-OIB); (b) first-line oxaliplatin/irinotecan + bevacizumab followed by second-line oxaliplatin/irinotecan + bevacizumab (OIB-OIB); (c) OI-OIB followed by a third-line targeted biologic (OI-OIB-TB); and (d) OIB-OIB followed by a third-line targeted biologic (OIB-OIB-TB) **Comparators:** Against each other	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** -	**Effect:** The incremental gains in QALYs in each strategy compared with OI-OIB: 0.23 (OIB-OIB); Dominated (OI-OIB-TB); 0.17 (OIB-OIB-TB) **Cost:** The incrental cost for each strategy in comparison with OI-OIB were: 28,113 (OIB-OIB); $21,709 (OI-OIB-TB); $68,247 (OIB-OIB-TB)	**ICER/ICUR:** OIB-OIB (vs. OI-OIB) was not cost-effective with an incremental cost-effectiveness ratio (ICER) per patient of $119,007/QALY; OI-OIB-TB (vs. OIB-OIB) was dominated; and OIB-OIB-TB (vs. OIB-OIB) was not cost-effective with an ICER of $405,857/QALY **Main conclusion:** Overall, survival increases marginally with the addition of targeted biologics, such as bevacizumab, at first line and third line at substantial costs. Treatment sequences with bevacizumab at first line and targeted biologics at third line may not be cost-effective at the commonly used threshold of $100,000/QALY gained, but a marginal decrease in the cost of bevacizumab may make treatment sequences with first-line bevacizumab cost-effective

7.14 **Colorectal cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
96	Economic evaluation study (CHEER-compliant): Cost-effectiveness analysis of RAS screening for treatment of metastatic colorectal cancer based on the CALGB 80405 trial.; Zhou J.; 2016; China	**Target Population:** Patients with metastatic colorectal cancer **Intervention:** Cetuximab and Bevacizumab, Cetuximab+FOLFIRI, Cetuximab+FOLFOX, Bevacizumab + FOLFIRI, Bevacizumab + FOLFOX **Comparators:** Against each other	**Perspective:** Payer and Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies, databases and clinical trial **WTP threshold:** $20,301/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The data in analysis 1 was 1.81 QALYs for KRAS-Cetux, 1.75 QALYs for KRAS-Bev, 1.91 QALYs for RAS-Cetux, and 1.87 for RAS-Bev. The effectiveness in analysis 2 was 1.94 QALYs for FOLFOX-Cetux, 1.74 QALYs for FOLFOX-Bev, 1.89 QALYs for FOLFIRI-Cetux, and 2.08 QALYs for FOLFIRI-Bev. **Cost:** In the Markov model 1, $159,993.30 for KRAS-Bev, $157,748.27 for KRAS-Cetux, and $140,920.25 for RAS-Bev. In the Markov model 2, $158,250.86 for FOLFOX-Cetux, $140,690.31 for FOLFOX-Bev, $152,319.29 for FOLFIRI-Cetux and $138,933.51 for FOLFIRI-Bev	**ICER/ICUR:** In analysis 1, the cost per QALY was $88,394.09 for KRAS-Cetux, $80,797.82 for KRAS-Bev, $82,590.72 for RAS-Cetux, and $75,358.42 for RAS-Bev.In analysis 2, the cost per QALY was $81,572.61, $80,856.50, $80,592.22, and $66,794.96 for FOLFOX-Cetux, FOLFOX-Bev, FOLFIRI-Cetux, and FOLFIRI-Bev, respectively. **Main conclusion:** It was economically favorable to identify patients with extended RAS-wt status. Furthermore, FOLFIRI plus Bev was the preferred strategy in extended RAS-wt patients.
97	Cost-Effectiveness Analysis of Different Sequences of the Use of Epidermal Growth Factor Receptor Inhibitors for Wild-Type KRAS Unresectable Metastatic Colorectal Cancer.; Riesco-Martínez MV.; 2016; Canada	**Target Population:** Unresectable wild-type KRAS metastatic colorectal cancer **Intervention:** strategy A (reference strategy): EGFRI monotherapy in third line (3L); ie, first-line [1L]: Bev + FOLFIRI [FP + I] or FOLFOX [FP + O]; second line [2L]: FOLFIRI/FOLFOX; 3L: EGFRI); **Comparators:** strategy B: EGFRI and I in 3L (ie, 1L: Bev + FOLFIRI/FOLFOX; 2L: FOLFIRI/FOLFOX; 3L: EGFRI + I); and strategy C: EGFRI in 1L (ie, 1L: EGFRI + FOLFIRI/FOLFOX; 2L: Bev + FOLFIRI/FOLFOX; 3L: best supportive care)	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Published studies, databases and clinical trials **WTP threshold:** CAD$ 130,000 **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** QALY of 1.48, 1.54, and 1.50 for strategies A, B, and C **Cost:** Strategy C was the most expensive, with a total cost of $203,275, whereas strategy A (reference strategy) was the least expensive at $133,390. Strategy B had a total cost of $140,687.	**ICER/ICUR:** The ICERs for strategy B and C were CAD$119,623 and CAD$3,176,591 compared with the reference strategy, respectively **Main conclusion:** First-line use of EGFRI in metastatic colorectal cancer is not cost effective at its current pricing relative to Bev.
98	Bevacizumab Continuation Versus Treatment Holidays After First-Line Chemotherapy With Bevacizumab in Patients With Metastatic Colorectal Cancer: A Health Economic Analysis of a Randomized Phase 3 Trial (SAKK 41/06).; Matter-Walstra K.; 2016; Switzerland	**Target Population:** Metastatic colorectal cancer patients **Intervention:** BEV continuation as a single agent **Comparators:** No BEV continuation as a single agent	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, clinical trials and published studies **WTP threshold:** CHF100,000/LYG and CHF75,000/LYG **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** -	**Effect:** - **Cost:** The total incurred mean costs per patient were 126,631 Swiss francs (CHF) for BEV versus CHF100,146 for no BEV	**ICER/ICUR:** CHF108,991/LYG **Main conclusion:** The clinical conclusion that BEV continuation as a single agent after completion of first-line chemotherapy is of low therapeutic value is supported by this health economic analysis. Costs increase without significant clinical benefit in this setting.

7.15 **Colorectal cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
99	Economic Analysis of Panitumumab Compared With Cetuximab in Patients With Wild-type KRAS Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy.; Graham CN.; 2016; United States	**Target Population:** Patients with wild-type KRAS (exon 2) metastatic colorectal cancer (mCRC) after previous chemotherapy treatment failure **Intervention:** Panitumumab **Comparators:** Cetuximab	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $50,000-$100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Semi-Markov Model	**Effect:** The model projected 1.072 life-years for panitumumab and 1.051 life-years for cetuximab. Adjusting for quality of life, panitumumab was estimated to produce 0.736 QALY, whereas cetuximab was estimated to produce 0.726 QALY **Cost:** Total drug costs for panitumumab were lower than total drug costs for cetuximab ($50,360 vs $56,377). Costs for administration, adverse events, and end-of-life care were also slightly lower for panitumumab than for cetuximab. However, costs for physician visits, monitoring for disease progression, and BSC were slightly higher for panitumumab than for cetuximab due to longer projected survival	**ICER/ICUR:** Scenario analyses indicated robust results, as modifications of key model assumptions consistently demonstrated panitumumab dominance. Furthermore, when accounting for uncertainty across all model parameters in the probabilistic sensitivity analysis, panitumumab was cost-effective at a willingness-to-pay threshold of $50,000 or more in >92% of model simulations in the cost-effectiveness analysis. **Main conclusion:** These economic analyses comparing panitumumab and cetuximab in chemorefractory wild-type KRAS (exon 2) mCRC suggest benefits in favor of panitumumab.
100	Cost-Effectiveness of Cetuximab as First-line Treatment for Metastatic Colorectal Cancer in the United States.; Shankaran V.; 2018; United States	**Target Population:** KRAS wild-type (WT) metastatic colorectal cancer (mCRC) **Intervention:** Cetuximab and FOLFIRI **Comparators:** Bevacizumab and FOLFIRI	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Published literature and clinical trials **WTP threshold:** $150,000/LY **Cost type:** **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Compared with bevacizumab, KRAS-WT patients receiving first-line cetuximab gained 5.7 months of life **Cost:** Those 5.7 months at a cost of $46,266	**ICER/ICUR:** KRAS WT: $97,223/LY or $122,610/QALY, extened RAS-WT patients $77,339/LY or $99,584/QALY **Main conclusion:** Our analysis of FIRE-3 data suggests that first-line treatment with cetuximab and FOLFIRI in KRAS (and extended RAS) WT mCRC patients may improve health outcomes and use financial resources more efficiently than bevacizumab and FOLFIRI.
101	Cost-effectiveness Analysis of Cetuximab in Treatment of Metastatic Colorectal Cancer in Iranian Pharmaceutical Market.; Davari M.; 2015; Iran	**Target Population:** Patients with unresectable metastatic CRC **Intervention:** Cetuximab + (FOLFIRI, FOLFOX, CAPOX) **Comparators:** FOLFIRI, FOLFOX, CAPOX	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** Published studies, databases and clinical trials **WTP threshold:** 3x GDP per capita ($12258x3) **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** -	**Effect:** The addition of cetuximab to FOLFIRI, FOLFOX and CAPOX programs increased PFS by 0.1, 0.042 and 0.042 years, respectively. Similarly, the addition of cetuximab to FOLFIRI, FOLFOX and CAPOX increased OS by 0.325, 0.442 and 0.442 years **Cost:** A total cost of also cost $212825 (Cet+FOLFIRI), $202484 (Cet+FOLFOX) and $204198 (Cet+CAPOX)	**ICER/ICUR:** FOLFIRI + cetuximab treatment program provides a better value for money with the cost of $859,756/PFLYG. CAPOX and FOLFOX programs plus cetuximab provide higher cost per additional PFLYG, respectively. **Main conclusion:** In summary, the results of this study confirm that the administration of FOLFOX in combination with cetuximab provides a better ICER compared to its alternatives in terms of LYG. However, according to the WHO suggested threshold, none of the cetuximab treatment programs could be considered cost-effective for the Iranian health care market.
102	First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis.; Goldstein DA.; 2015; United States	**Target Population:** Patientes with previously untreated metastatic colorectal cancer **Intervention:** 1. Fluorouracil, leucovorin, and oxaliplatin with bevacizumab in the first-line treatment 2. Fluorouracil, leucovorin, and irinotecan with bevacizumab in the second-line of treatment **Comparators:** 1. Fluorouracil, leucovorin, and oxaliplatin in the first-line treatment 2. Fluorouracil, leucovorin, and irinotecan as second-line treatment	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** Clinical trials, published studies and database **WTP threshold:** $50,000-$100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Using bevacizumab in first-line therapy provided an additional 0.10 QALYs (0.14 life-years) and continuing bevacizumab beyond progression provided an additional 0.11 QALYs (0.16 life-years) **Cost:** Using bevacizumab in first-line therapy had a cost of $571,240/QALY and continuing beyond progression a cost of $364,083/QALY	**ICER/ICUR:** $571,240/QALY for first line regimen and $364,083/QALY for second line **Main conclusion:** Bevacizumab provides minimal incremental benefit at high incremental cost per QALY in both the first- and second-line settings of metastatic colorectal cancer treatment.

7.16 **Colorectal cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
103	Cost-effectiveness analysis of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer.; Graham CN.; 2014; France	**Target Population:** First-line treatment of patients with wild-type RAS metastatic colorectal cancer **Intervention:** Panitumumab plus mFOLFOX6 (oxaliplatin, 5-fluorouracil and leucovorin) **Comparators:** Bevacizumab + mFOLFOX6	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** €40,000-€60,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 4%/year **Approach:** Semi-Markov Model	**Effect:** Adjusting for quality of life, panitumumab plus mFOLFOX6 was estimated to produce 2.68 QALYs, while bevacizumab plus mFOLFOX6 was estimated to produce 2.05 QALYs **Cost:** Due to greater PFS (longer duration of therapy) and higher drug-acquisition costs, total drug costs were higher for panitumumab plus mFOLFOX6 than for bevacizumab plus mFOLFOX6 (€42,843 versus €29,871).	**ICER/ICUR:** 36,577€/QALY **Main conclusion:** The incremental cost per QALY gained indicates that panitumumab plus mFOLFOX6 represents good value for money in comparison to bevacizumab plus mFOLFOX6 and, with a willingness-to-pay ranging from €40,000 to €60,000, can be considered cost-effective in first-line treatment of patients with wild-type RAS mCRC.
104	Cost-effectiveness of first-line treatments for patients with KRAS wild-type metastatic colorectal cancer.; Ewara Em.; 2014; Canada	**Target Population:** First-line treatments for patients with KRAS wild-type metastatic colorectal cancer **Intervention:** Bevacizumab + FOLFIRI **Comparators:** Panitumumab + FOLFIRI, Cetuximab + FOLFIRI	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** Compared with bevacizumab plus folfiri, first-line treatment with panitumumab plus folfiri resulted in an incremental loss of 0.033 QALYs; treatment with cetuximab plus folfiri resulted in an incremental loss of 0.008 QALYs **Cost:** Compared with bevacizumab plus folfiri, an incremental cost of $23,359 per person was found; treatment with cetuximab plus folfiri resulted in an incremental cost of $3,159 per person.	**ICER/ICUR:** Bevacizumab + FOLFIRI dominated the other two first-line treatment options. **Main conclusion:** Evidence from Ontario showed that bevacizumab plus folfiri is the cost-effective first-line treatment strategy for patients with KRAS wild-type mcrc.
105	The cost effectiveness of bevacizumab when added to capecitabine, with or without mitomycin-C, in first line treatment of metastatic colorectal cancer: results from the Australasian phase III MAX study.; Carter HE.; 2014; Australia	**Target Population:** First-line treatment of Metastatic Colorectal Cancer **Intervention:** Bevacizumab + Capecitabine **Comparators:** Capecitabine	**Perspective:** Payer **Time Horizon:** 1,5 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/year **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Decision Analytical Model	**Effect:** The intervention resulted in an additional 0,154 years of QAPFS against the comparator **Cost:** Patients treated with bevacizumab + capecitabine accumulated an average cost of $44,169 per patient against $14,557 when only treated with capecitabine alone.	**ICER/ICUR:** $192,156/QAPFS **Main conclusion:** Bevacizumab was not found to be cost effective at its listed price, based on results from the MAX trial.
106	Comparative cost-effectiveness of bevacizumab-irinotecan-fluorouracil versus irinotecan-fluorouracil in first-line metastatic colorectal cancer.; Ruiz-Millo; 2014; Spain	**Target Population:** Treatment-naïve metastatic colorectal cancer patients **Intervention:** Bevacizumab + Irinotecan + Fluorouracil **Comparators:** Irinotecan + Fluorouracil	**Perspective:** - **Time Horizon:** 4 years **Parameter Sources:** Database and medical records **WTP threshold:** - **Cost type:** - **Discount Rates:** - **Approach:** -	**Effect:** The median PFS was 10.05 months in the CPT-FUFA group and 11.04 months in the Bevacizumab_CPTFUFA group **Cost:** As used in our clinical setting but in addition represents an increase in costs of 12,696.5 euros/patient treated in our study population.	**ICER/ICUR:** Since the effectiveness response variables are equivalent, the cost-effectiveness analysis has been simplified into a cost-minimization analysis. **Main conclusion:** The addition of bevacizumab to the irinotecan-fluorouracil regimen, does not improve progression-free survival in our study population but increases costs per treated patient. These results potentially compromise the cost-effectiveness of the Bevacizumab_CPT-FUFA regimen.

7.17 **Endometrial cancer Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
107	Pembrolizumab in advanced recurrent endometrial cancer: A cost-effectiveness analysis.; Barrington DA.; 2019; United States	**Target Population:** Women with recurrent endometrial cancer that have failed first-line chemotherapy **Intervention:** Pembrolizumab **Comparators:** Pegylated liposomal doxorubicin/Bevacizumab	**Perspective:** - **Time Horizon:** - **Parameter Sources:** **WTP threshold:** $100,000/year OS **Cost type:** Drug medical costs **Discount Rates:** - **Approach:** -	**Effect:** In the MSI-H cohort the number of 2 year survivors yelded by the pembrolizumab arm was 507, 317 for bevacizumab and 158 for the PLD. In the non MSI-H cohort the number of 2 year survivors yelded by the pembrolizumab arm was 1804, 1443 for bevacizumab and 722 for the PLD. **Cost:** In the MSI-H cohort the cost yelded by the pembrolizumab arm was $57.9 million (M) and $30.5 M for bevacizumab and $6 M for the PLD. In the non MSI-H cohort the cost yelded by the pembrolizumab arm was $318.3 M, $137.4 M for bevacizumab and $27.2 M for the PLD.	**ICER/ICUR:** Non-MSI-H : ICER(vs PLD)= $153,028 ICER (vs Bevacizumab)= $341,830 MSI-H : MSI-H patients: ICER(vs PLD)=$147,249, Dominated vs bevacizumab **Main conclusion:** For patients with MSI-H recurrent endometrial cancers who have failed first-line chemotherapy, pembrolizumab is cost-effective relative to other single agent drugs

7.18 **Esophageal cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
108	Cost-Effectiveness of Cetuximab for Advanced Esophageal Squamous Cell Carcinoma.; Jannaat VT.; 2016; Netherlands	**Target Population:** Patients with advanced esophageal squamous cell carcinoma **Intervention:** Cetuximab + cisplatin +5-fluorouracil **Comparators:** Cisplatin +5-fluorouracil	**Perspective:** Payer **Time Horizon:** 0.9 years **Parameter Sources:** Published studies, Clinical trials and database **WTP threshold:** €40,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** -	**Effect:** The mean survival gained by the addition of cetuximab to standard chemotherapy was 0.187 life years and 0.105 QALYs. **Cost:** The mean incremental cost was calculated to be € 26,459 per treated patient.	**ICER/ICUR:** €252,203/QALY **Main conclusion:** Addition of cetuximab to a cisplatin-5-fluorouracil first-line regimen for advanced esophageal squamous cell carcinoma is not cost-effective when appraised according to currently accepted criteria.

7.19 **Gastric cancer Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
109	Cost-effectiveness of Paclitaxel + Ramucirumab Combination Therapy for Advanced Gastric Cancer Progressing After First-line Chemotherapy in Japan.; Saito S.; 2017; Japan	**Target Population:** Second-line treatment in patients with advanced gastric cancer **Intervention:** Ramucirumab + Paclitaxel **Comparators:** Paclitaxel	**Perspective:** Payer **Time Horizon:** 3 years **Parameter Sources:** Published studies, clinical trials and database **WTP threshold:** ¥12 million/QALY **Cost type:** Direct medical costs **Discount Rates:** 2%/year **Approach:** Markov Model	**Effect:** Paclitaxel + ramucirumab combination therapy was estimated to provide an additional 0.09 QALYs (0.10 LYs) **Cost:** A estimated cost of ¥3,870,077 for the Paclitaxel + Ramucirumab	**ICER/ICUR:** ¥43,010,248/QALY **Main conclusion:** Adding ramucirumab to a regimen of paclitaxel in the second-line treatment of advanced gastric cancer is expected to provide a minimal incremental benefit at a high incremental cost per QALY
110	Cost-effectiveness and safety of ramucirumab plus paclitaxel chemotherapy in the treatment of advanced and recurrent gastric cancer.; Kimura M.; 2018; Japan	**Target Population:** Patients with advanced and recurrent gastric cancer **Intervention:** Ramucirumab + Paclitaxel (Ram + PTX) **Comparators:** Paclitaxel (PTX), Irinotecan (CPT-11)	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** Database and published studies **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** -	**Effect:** The median survival time in months considered for the different regimens were: 8.5 (PTX); 8.0 (CPT) and 10.9 (Ram + PTX) **Cost:** The expected costs considered for the different regimens were: JPY 725,864.5 (PTX); JPY 1,061,883.0 (CPT) and JPY 7,398,902.2 (Ram + PTX)	**ICER/ICUR:** Ram + PTX regimen to the PTX regimen, JPY 2,780,432.4/MST ; Ram + PTX regimen to the CPT-11 regimen, JPY 2,185,179.0/MST **Main conclusion:** The Ram+PTX regimen is less cost-effective compared to both the PTX and CPT-11 regimens, but the Ram+PTX regimen is a well tolerated regimen with sufficient efficacy.
111	Cost-Effectiveness Analysis of Second-Line Chemotherapy Agents for Advanced Gastric Cancer; Lam SW.; 2017; United States	**Target Population:** Patients with advanced gastric cancer who have failed previous chemotherapy **Intervention:** Irinotecan, Docetaxel, Paclitaxel, Ramucirumab, Paclitaxel + Ramucirumab and palliative care. **Comparators:** Against each other	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** $50,000-$160,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** - **Cost:** -	**ICER/ICUR:** Docetaxel, ramucirumab alone, and palliative care were dominated strategies. Paclitaxel and the combination of paclitaxel plus ramucirumab led to higher QALYs gained, at an incremental cost of $86,815 and $1,056,125 per QALY gained, respectively **Main conclusion:** Irinotecan alone appears to be the most cost-effective second-line regimen for patients with gastric cancer. Paclitaxel may be cost-effective if the WTP threshold was set at $160,000/QALY gained.

7.20 **Head and Neck cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
112	Cost-effectiveness of nivolumab in the treatment of head and neck cancer.; Hirschmann A.; 2018; Switzerland	**Target Population:** Second-line treatment for r/mHNSCC **Intervention:** Nivolumab **Comparators:** Cetuximab, Methotrexate, Docetaxel	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Database and clinical trials **WTP threshold:** CHF100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Markov Model	**Effect:** We estimated an incremental effectiveness of 0.35 QALYs **Cost:** We estimated incremental costs of CHF 35,562 with nivolumab	**ICER/ICUR:** CHF 102,957/QALY **Main conclusion:** At current prices nivolumab has an ICER of around CHF 100,000 per QALY gained in the second line treatment of r/mHNSCC patients in Switzerland.
113	Cost-effectiveness analysis of salvage therapies in locoregional previously irradiated head and neck cancer.; Kim H.; 2018; United States	**Target Population:** Patients with recurrent head and neck cancer. **Intervention:** chemotherapy + cetuximab **Comparators:** platinum-based chemotherapy; stereotactic body radiotherapy (SBRT) alone; SBRT + cetuximab; intensity-modulated radiotherapy + chemotherapy	**Perspective:** Societal **Time Horizon:** 3 years **Parameter Sources:** **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Markov Model	**Effect:** The median overall survival was assumed to be 10 months for all treatment strategies except for chemotherapy alone (7 months). **Cost:** $4290 for 6 cycles of platinum-based chemotherapy alone; $73 880 for 6 cycles of chemotherapy plus 18 cycles of cetuximab; $16 500 for 5 fractions of SBRT alone; $26 500 for 5 fractions of SBRT plus 3 cycles of cetuximab; and $24 290 for 33 fractions of IMRT plus 6 cycles of chemotherapy. In addition, 1-day hospitalization cost was estimated as $2200.	**ICER/ICUR:** In the base case analysis, no treatment strategy was cost-effective at a WTP threshold. The most cost-effective therapy was SBRT alone with $150 866 per QALY gained **Main conclusion:** None of the treatment strategies were cost-effective. However, SBRT-based reirradiation has potential to be cost-effective.
114	Cost-effectiveness Analysis of Nivolumab for Treatment of Platinum-Resistant Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck.; Tringale KR.; 2018; United States	**Target Population:** Patients with recurrent or metastatic platinum-refractory HNC **Intervention:** Nivolumab **Comparators:** Standard single-agent therapy	**Perspective:** Payer and Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Our base case model found that treatment with nivolumab improved effectiveness by 0.400 QALYs compared with standard therapy **Cost:** Our base case model found that treatment with nivolumab increased overall cost by $117 800 compared with standard therapy	**ICER/ICUR:** $294 400/QALY **Main conclusion:** While nivolumab improves overall survival, at its current cost it would not be considered a cost-effective treatment option for patients with HNC.

7.21 **Head and Neck cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
115	Cost-effectiveness of nivolumab for recurrent or metastatic head and neck cancer ☆; Ward MC.; United States	**Target Population:** Patients with platinum-refractory recurrent or metastatic head and neck cancer **Intervention:** Nivolumab **Comparators:** Single-agent cetuximab, methotrexate or docetaxel and first testing for PD-L1 to select for nivolumab	**Perspective:** Payer **Time Horizon:** 3 years **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Overall analysis of the base case scenario (nivolumab vs. physician choice of mixed standard therapies) demonstrated that the use of nivolumab was more effective than standard therapy by 0.337 QALYs. **Cost:** Nivolumab was also more expensive, with an average cost of $73,463 compared to $26,133 for standard treatment (+$47,329)	**ICER/ICUR:** When comparing nivolumab to the standard arm of CheckMate, nivolumab demonstrated an incremental cost-effectiveness ratio (ICER) of $140,672/QALY. Treatment selection by PD-L1 immunohistochemistry did not markedly improve the cost-effectiveness of nivolumab. **Main conclusion:** Nivolumab is preferred to single-agent cetuximab but requires a willingness-to-pay of at least $150,000/QALY to be considered cost-effective when compared to docetaxel or methotrexate. Selection by PD-L1 does not markedly improve the cost-effectiveness of nivolumab. This informs patient selection and clinical care-path development.
116	Cost-Effectiveness of Nivolumab in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma.; Zargar M.; 2018; Canada	**Target Population:** Patients with platinum-refractory, recurrent, metastatic head and neck squamous cell carcinoma (r/m HNSCC) **Intervention:** Nivolumab **Comparators:** Docetaxel	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 1,5%/year **Approach:** State Trasition Model	**Effect:** Nivolumab extended mean OS by 4 months compared with docetaxel and resulted in fewer treatment-related adverse events, producing an incremental effectiveness of 0.13 quality-adjusted life years (QALY) **Cost:** The incremental cost of treatment with nivolumab was $18,823.	**ICER/ICUR:** $144,744/QALY **Main conclusion:** We conclude that although nivolumab offers clinical benefit for the treatment of r/m HNSCC over current regimens, it is not cost-effective based on its list price. We have also established a value-based price estimate for nivolumab to be cost-effective in this patient population. Further study is required to draw a definitive conclusion on biomarkers for cost-effectiveness.
117	Real-world cost-effectiveness of cetuximab in locally advanced squamous cell carcinoma of the head and neck; Van der Linden N.; 2015; Netherlands	**Target Population:** Locally advanced squamous cell carcinoma of the head and neck. **Intervention:** Cetuximab + Radiotherapy **Comparators:** Radiotherapy	**Perspective:** Payer **Time Horizon:** 5 years, 10 years and Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** €80,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 0% and 4% / year (C) and 0% and 1,5% /year (O) **Approach:** Markov Model	**Effect:** Prolonged median locoregional control (24.4 vs. 14.9 months), progression-free survival (17.1 vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) for patients who receive cetuximab added to the comparator radiotherapy **Cost:** Mean total treatment costs were estimated at €24,714 (SD €9,695) and €12,862 (SD €11,713) in the RT+C and in the comparator group, respectively.	**ICER/ICUR:** €14,624 - €38,543/QALY **Main conclusion:** Current results show the combined treatment of radiotherapy + cetuximab to be a cost-effective treatment option for patients with LA SCCHN.

7.22 **Leukemia Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
118	Economic evaluation of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia; Nam J.; 2018; Canada	**Target Population:** Newly-diagnosed Philadelphia chromosome-negative, CD20-positive, B-cell precursor ALL **Intervention:** Rituximab + SoC chemotherapy **Comparators:** SoC chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** CAN$100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 1,5%/year **Approach:** Decision Analytical	**Effect:** Quality-adjusted life-years (QALYs) increased by 2.20 QALYs with rituximab in addition to SOC. **Cost:** Total costs were higher with rituximab added to SOC vs. SOC alone ($190,637 vs. $142,529; difference=$48,108).	**ICER/ICUR:** CAN$21,828/QALY **Main conclusion:** For adults with ALL, rituximab in addition to SOC was found to be a cost-effective intervention, compared to SOC alone. The addition of rituximab is associated with increased life years and increased QALYs at a reasonable incremental cost.
119	Cost-Effectiveness of Ibrutinib Compared With Obinutuzumab With Chlorambucil in Untreated Chronic Lymphocytic Leukemia Patients With Comorbidities in the United Kingdom.; Sinha R.; 2018; United Kingdom	**Target Population:** Untreated patients with chronic lymphocytic leukemia with comorbidities who cannot tolerate fludarabine-based therapy **Intervention:** Ibrutinib **Comparators:** Obinituzumab + chlorambucil	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials, published studies and database **WTP threshold:** £20,000-£30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Semi-Markov Model	**Effect:** An average gain of 1.49 QALYs was estimated for ibrutinib compared with G-Clb **Cost:** An average additional cost of £112,835 per patient was considered.	**ICER/ICUR:** £75,648 and £-143,279/QALY **Main conclusion:** As per base-case analyses, an adequate discount on ibrutinib is required to make it cost-effective as per the UK thresholds. The scenario analysis substantiates ibrutinib's cost-savings for the UK National Health Services and advocates patient's access to ibrutinib in the UK.
120	Cost-utility analysis of idelalisib in combination with rituximab in relapsed or refractory chronic lymphocytic leukaemia; Casado LF.; 2018; Spain	**Target Population:** Patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL) **Intervention:** Rituximab + Idelalisib **Comparators:** Rituximab	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** €45,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** Compared to R, 2L IR treatment resulted in QALY gain of 3.147 (4.965 versus 1.818). **Cost:** Total costs were €118 254 for IR versus €23 874 for R.	**ICER/ICUR:** €29,990/QALY **Main conclusion:** IR can be considered a cost-effective treatment compared to R, in the treatment of R/R CLL patients for the Spanish NHS.
121	Cost-Effectiveness Analysis of Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukaemia in Portuguese Patients who are Unsuitable for Full-Dose Fludarabine-Based Therapy; Paquete AT.; 2017; Portugal	**Target Population:** Previously untreated Chronic Lymphocitic Leukemia patients who are unsuitable for full-dose fludarabine-based therapy **Intervention:** Obinutuzumab + chlorambucil (GClb), Rituximab + chlorambucil (RClb) **Comparators:** Chlorambucil (Clb)	**Perspective:** Payer **Time Horizon:** 25 years **Parameter Sources:** Database, Published studies and clinical trials **WTP threshold:** €30,000-€40,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** GClb and RClb were associated with an increase of 1.06 and 0.39 quality-adjusted life-years (QALY) when compared to Clb. **Cost:** GClb and RClb were associated with an additional cost of €21,720 and €9836 when compared to Clb, respectively	**ICER/ICUR:** GClb versus Clb was €20,397/QALY, while RClb was extendedly dominated. **Main conclusion:** The use of GClb for previously untreated CLL patients who are unsuitable for full-dose fludarabine-based therapy incurs an incremental cost per QALY that is generally accepted in Portugal. Therefore, although there is some uncertainty, obinutuzumab is probably a cost-effective therapy in the Portuguese setting.
122	Cost-effectiveness of obinutuzumab for chronic lymphocytic leukaemia in The Netherlands.; Blommestein HM.; 2016; Netherlands	**Target Population:** Chronic lymphocytic leukaemia **Intervention:** Obinutuzumab combined with chlorambucil (GClb) **Comparators:** Rituximab + chlorambucil (RClb) and chlorambucil (Clb) and ofatumumab + chlorambucil (OClb)	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** **WTP threshold:** €50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model	**Effect:** An incremental gain of 1.06 and 0.64 QALYs was estimated for GClb compared to Clb and RClb respectively.Indirect treatment comparisons showed an incremental gain varying from 0.44 to 0.77 QALYs for GClb compared to OClb. **Cost:** GClb compared to Clb and RClb showed additional costs of €23,208 and €7254 per patient, while GClb compared to OClb revealed additional costs varying from €7041 to €5028 per patient.	**ICER/ICUR:** €21,823/QALY (vs Clb) and €11,344/QALY (RClb) and €6,556-€16,180/QALY (vs Oclb) **Main conclusion:** GClb appeared to be a cost-effective treatment strategy compared to RClb, OClb and Clb.

7.23 **Leukemia Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
123	Cost-Effectiveness Model for Chemoimmunotherapy Options in Patients with Previously Untreated Chronic Lymphocytic Leukemia Unsuitable for Full-Dose Fludarabine-Based Therapy; Becker U.; 2016; United Kingdom	**Target Population:** Previously Untreated Chronic Lymphocytic Leukemia Unsuitable for Full-Dose Fludarabine-Based Therapy **Intervention:** Obinutuzumab + chlorambucil **Comparators:** Rituximab + chlorambucil or chlorambucil	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** £30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Markov Model	**Effect:** GClb was projected to result in gains in discounted life expectancy, ranging from an increase of 1.199 years compared with Clb to 0.675 years compared with RClb **Cost:** Total costs in treatment with GClb were projected to have increased by £26,927 and £14,827 compared with those in Clb and RClb treatments, respectively	**ICER/ICUR:** GClb versus RBenda (£13,747/QALY), OClb (£15,431/QALY), and RClb (£22,905/QALY). GClb compared with Clb monotherapy (£25,318/QALY) and Benda (£28,686/QALY). **Main conclusion:** GClb was estimated to increase both quality-adjusted life expectancy and treatment costs compared with several commonly used therapies, with incremental cost-effectiveness ratios below commonly referenced UK thresholds. This article offers a real example of how to combine direct and indirect evidence in a cost-effectiveness analysis of oncology drugs.
124	Cost-effectiveness of First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable.; Soini E.; 2016; Finland	**Target Population:** First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable **Intervention:** Obinutuzumab + Chlorambucil; Ofatamumab + Chlorambucil; Rituximab + Chlorambucil; Rituximab + Bendamustine **Comparators:** Cholrambucil	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published Studies, database and clinical trials **WTP threshold:** €30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The discounted quality-adjusted survival were 2.71 (Clb), 2.93 (OClb), 3.10 (RB), 3.11 (RClb) and 3.75 (GClb). **Cost:** The lifetime costs were €12,159 (Clb), €29,690 (OClb), €34,972 (RB), €29,810 (RClb) and €42,467 (GClb)	**ICER/ICUR:** Compared with the most affordable treatment (Clb) were as follows: GClb, €29,334; RClb, €43,958; RB, €59,316; and OClb, €82,159. **Main conclusion:** With €30,000/QALY gained or higher thresholds, GClb was clearly the most cost-effective CLL treatment when RFC was unsuitable. In general, GClb provided the best value for money option in terms of relative and absolute outcomes. The low to moderate value of additional research or loss from a wrong decision was assessed.
125	Cost-effectiveness of rituximab in addition to fludarabine and cyclophosphamide (R-FC) for the first-line treatment of chronic lymphocytic leukemia.; Müller D.; 2016; Germany	**Target Population:** First line treatment of chronic lymphocytic leukemia **Intervention:** Rituximab + Fludarabine + Cyclophosphamide **Comparators:** Fludarabine + Cyclophosphamide	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and clinical trials **WTP threshold:** €88,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The addition of rituximab to FC chemotherapy results in a gain of 1.1 QALYs. **Cost:** Additional costs for the firstline treatment of CLL over 6 cycles amounted to €20,266.	**ICER/ICUR:** €17,979/QALY **Main conclusion:** From the German SHI perspective, rituximab in combination with FC chemotherapy represents good value for first-line treatment of patients with CLL and compares favorably with chemotherapy alone.
126	Cost Effectiveness of Ofatumumab Plus Chlorambucil in First-Line Chronic Lymphocytic Leukaemia in Canada.; Herring W.; 2016; Canada	**Target Population:** Patients with chronic lymphocytic leukaemia for whom fludarabine-based therapies are considered inappropriate **Intervention:** Ofatumumab + Chlorambucil **Comparators:** Chlorambucil	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** **WTP threshold:** CAN$100,000/QALY **Cost type:** Published studies and clinical trials **Discount Rates:** 5%/year **Approach:** Semi-Markov Model	**Effect:** First-line treatment with OChl led to an increase in 0.41 QALYs **Cost:** First-line treatment with OChl led to an increase in total costs of $Can27,866	**ICER/ICUR:** CAN$68,647/QALY **Main conclusion:** Base-case results indicated that improved overall response and PFS for OChl compared with chlorambucil translated to improved quality-adjusted life expectancy.
127	Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia in Ukraine.; Mandrink O.; 2015; Ukraine	**Target Population:** Chronic lymphocytic leukemia. **Intervention:** Rituximab + Fludarabine + Cyclophosphamide **Comparators:** Fludarabine + Cyclophosphamide	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources: Published studies, clinical** trials and database **WTP threshold:** Three times GDP (3xUS$3,900) **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The incremental QALYs for treatment-naïve patients was 1.24 and 1.18 for refractory/relapsed patients **Cost:** The incremental cost for treatment-naïve patients was US$10,827 and US$13,081 for refractory/relapsed patients.	**ICER/ICUR:** US$8,704/QALY for treatment-naïve patients and US$11,056/QALY for refractory/relapsed patients **Main conclusion:** State coverage of rituximab treatment may be considered a cost-effective treatment for the Ukrainian population under conditions of economic stability, cost-effectiveness threshold growth, or rituximab price negotiations.

7.24 **Leukemia Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
128	Modelling the cost effectiveness of rituximab in chronic lymphocytic leukaemia in first-line therapy and following relapse.; Adena M.; 2014; Australia	**Target Population:** Chronic lymphocytic leukaemia in first-line therapy and following relapse **Intervention:** Rituximab + Fludarabine + Cyclophosphamide (R-FC) **Comparators:** Fludarabine + Cyclophosphamide (FC)	**Perspective:** Payer **Time Horizon:** 15 years **Parameter Sources:** Published studies and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** The addition of rituximab results in an incremental gain of 0.94 QALYs. **Cost:** The incremental cost associated with the addition of rituximab is AUS $40,268.8.	**ICER/ICUR:** AUS $42,906/QALY **Main conclusion:** Rituximab, in combination with chemotherapy, when used multiple times throughout the treatment algorithm, appears to be cost effective for CLL from the Australian healthcare perspective, with a cost/QALYG within the range generally accepted as providing value.
129	Cost-effectiveness of blinatumomab versus salvage chemotherapy in relapsed or refractory Philadelphia-chromosome-negative B-precursor acute lymphoblastic leukemia from a US payer perspective.; Delea TE.; 2017; United States	**Target Population:** Adults with relapsed or refractory (R/R) Philadelphia-chromosome-negative (Ph-) B-precursor acute lymphoblastic leukemia (ALL) **Intervention:** Blinatumomab **Comparators:** Salvage Chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, clinical trials and database **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** The B-GEM projected blinatumomab to yield 1.92 additional life years and 1.64 QALYs. **Cost:** An incremental cost of $180,642 was estimated compared with SoC.	**ICER/ICUR:** $110,108/QALY **Main conclusion:** Compared with SOC, blinatumomab is a cost-effective treatment option for adults with R/R Ph - B-precursor ALL from the US healthcare perspective at an ICER threshold of $150,000 per QALY gained. The value of blinatumomab is derived from its incremental survival and health-related quality-of-life (HRQoL) benefit over SOC.

7.25 **Lymphoma: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
130	Cost-effectiveness of axicabtagene ciloleucel for adult patients with relapsed or refractory large B-cell lymphoma in the United States.; Roth JA.; 2018; United States	**Target Population:** Adult patients with relapsed or refractory large B-cell lymphoma **Intervention:** Axicabtagene ciloleucel **Comparators:** Salvage Chemotherapy (R-DHAP)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical	**Effect:** In the base case, LYs, QALYs, and were 9.5 and 7.7 for axi-cel vs 2.6, and 1.1, for salvage chemotherapy, respectively. **Cost:** In the base case, lifetime costs were $552,921 for axi-cel vs $172,737 for salvage chemotherapy.	**ICER/ICUR:** $58,146/QALY **Main conclusion:** Axi-cel is a potentially cost-effective alternative to salvage chemotherapy for adults with R/R LBCL. Long-term follow-up is necessary to reduce uncertainties about health outcomes.
131	Exploring the potential cost-effectiveness of precision medicine treatment strategies for diffuse large B-cell lymphoma.; Chen Q.; 2018; United States	**Target Population:** Activated B-cell-like (ABC) diffuse large B-cell lymphoma (DLBCL) **Intervention:** subtype testing followed by RCHOP for Germinal Center B cell like + lenalidomide + RCHOP and **Comparators:** Standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** -	**Effect:** RCHOP provided 9.85 QALYs (12.19 LYs) and GEP testing provided 12.02 QALYs (14.82 LYs) **Cost:** RCHOP had a estimated cost of $53,406; while subtype-based treatment guided by GEP testing provided cost was estimated on $86,104	**ICER/ICUR:** $15,015/QALY **Main conclusion:** Although our exploratory analyses demonstrated a wide range of conditions where subtype-based treatment remained cost-effective, data from phase 3 trials are needed to validate our models' findings and draw definitive conclusions.
132	Real world costs and cost-effectiveness of Rituximab for diffuse large B-cell lymphoma patients: a population-based analysis.; Khor S.; 2014; Canada	**Target Population:** Diffuse large B-cell lymphoma patients **Intervention:** Rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy **Comparators:** CHOP Chemotherapy	**Perspective:** Payer **Time Horizon:** 3 years and 5 years **Parameter Sources:** Database and historical cohort **WTP threshold:** €100,000/LYG **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** -	**Effect:** RCHOP was associated with a mean absolute survival gain of approximately 1.3 months at three years and 3.2 months at five years. Age was associated with reductions in survival in both treatment arms in the 3- and 5-year timeframes. **Cost:** The incremental costs for RCHOP were $15,421 over 3 years and $16,298 over 5 years.	**ICER/ICUR:** $134,136/LY (3 years) and $61,984 per LYG (5 years) **Main conclusion:** Our results showed that the addition of rituximab to standard CHOP chemotherapy was associated with improvement in survival but at a higher cost, and was potentially cost-effective by standard thresholds for patients <60 years old. However, cost-effectiveness decreased significantly with age, suggesting that rituximab may be not as economically attractive in the very elderly on average. This has important clinical implications regarding age-related use and funding decisions on this drug.
133	Cost-effectiveness of obinutuzumab plus bendamustine followed by obinutuzumab monotherapy for the treatment of follicular lymphoma patients who relapse after or are refractory to a rituximab-containing regimen in the US.; Guzauskas GF.; 2018; United States	**Target Population:** Follicular lymphoma (FL) patients who relapsed after, or are refractory to (R/R), a rituximab-containing regimen **Intervention:** Obinutuzumab + Bendamustine **Comparators:** Bendamustine	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** State Trasition Model	**Effect:** G + B resulted in an increase in QALYs relative to B-monotherapy of 1.24.. **Cost:** G + B had an incremental total cost was $58,100.	**ICER/ICUR:** $47,000/QALY **Main conclusion:** This US-based analysis suggests that treatment with G + B compared to B-monotherapy is likely cost-effective in R/R-rituximab FL patients
134	The cost-effectiveness of immediate treatment or watch and wait with deferred chemotherapy for advanced asymptomatic follicular lymphoma.; Prettyjohns M.; 2018; United Kingdom	**Target Population:** Patients with advanced asymptomatic follicular lymphoma **Intervention:** Rituximab induction + maintenance and Watch and wait **Comparators:** Rituximab induction	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Non-published studies, published studies, database and clinical trials **WTP threshold:** £20,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Markov Model	**Effect:** The Rituximab induction strategy yelded a total of 11,31 QALYs, while R-I&M strategy resulted in an incremental gain of 0,14 QALYs and the watch and wait resulted in -0,33 **Cost:** The total cost of the comparator strategy was £38,355, while there was found an incremental cost of £9,614 with th R-I&M strategy and £9,793 with the watchful waiting strategy	**ICER/ICUR:** £69,406/QALY (R-I&M) and Watch and wait strategy was dominated **Main conclusion:** In conclusion, active treatment with rituximab induction is a cost-effective strategy to adopt in patients with asymptomatic follicular lymphoma.

7.26 **Lymphoma: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
135	Cost-Effectiveness Analysis of Bendamustine Plus Rituximab as a First-Line Treatment for Patients with Follicular Lymphoma in Spain.; Sabater E.; 2016; Spain	**Target Population:** First-Line Treatment for Patients with Follicular Lymphoma **Intervention:** Rituximab + Bendamustine **Comparators:** R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone)	**Perspective:** Payer **Time Horizon:** 25 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** €30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Health benefits were higher for rituximab-bendamustine treatment (10.31 QALYs) than for R-CHOP treatment (9.82 QALYs) **Cost:** At the end of the 25-year period, the rituximab-bendamustine first-line strategy had a total cost of €68,357 compared with €69,528 for R-CHOP.	**ICER/ICUR:** Rituximab + Bendamustine was dominant **Main conclusion:** First-line therapy with rituximab-bendamustine in FL patients was the dominant strategy over treatment with R-CHOP; it showed cost savings and higher health benefits for the Spanish NHS.
136	Frontline rituximab monotherapy induction versus a watch and wait approach for asymptomatic advanced-stage follicular lymphoma: A cost-effectiveness analysis.; Prica A.; 2015; Canada	**Target Population:** Assymptomatic advanced-stage follicular lymphoma **Intervention:** Rituximab induction (RI) with or without rituximab maintenance (RM) **Comparators:** Watch and wait	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies and database **WTP threshold:** $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** RI was the cheapest strategy. It was less costly at $59,953 versus $67,489 for the RM arm and $75,895 for the WW arm. **Cost:** RI was also associated with a slightly lower quality-adjusted life expectancy at 6.16 QALYs versus 6.28 QALYs for the RM strategy but was superior to WW (5.71 QALYs)	**ICER/ICUR:** $62,360/QALY vs RI. WW arm was dominated by both strategies. **Main conclusion:** RI without maintenance for asymptomatic advanced-stage follicular lymphoma is the preferred strategy: it minimizes costs per patient over a lifetime horizon.
137	Comparing the cost-effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma.; Chen Q.; 2015; United States	**Target Population:** Advanced-stage follicular lymphoma patients **Intervention:** Rituximab (MR) and Radioimmunotherapy (RI) **Comparators:** Observation	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Compared with observation, MR provided an additional 1.089 QALYs (1.099 LYs) and 1.399 QALYs (1.391 LYs) on the basis of the PRIMA trial and the ECOG trial, respectively, and RIT provided an additional 1.026 QALYs (1.034 LYs) **Cost:** The incremental cost per QALY gained was $40,335 (PRIMA) or $37,412 (ECOG) for MR and $40,851 for RIT.	**ICER/ICUR:** For RM $40,335/QALY and $37,412/QALY-gained in PRIMA and ECOG study, respectively, and for RIT was $40,851/QALY **Main conclusion:** MR and RIT following frontline FL therapy demonstrated favorable and similar cost-effectiveness profiles. The model results should be interpreted within the specific clinical settings of each trial. Selection of MR, RIT, or observation should be based on patient characteristics and expected trade-offs for these alternatives.
138	Cost-effectiveness of rituximab as maintenance treatment for relapsed follicular lymphoma: results of a population-based study.; Blommstein HM.; 2014; Netherlands	**Target Population:** Relapsed or refractory follicular lymphoma patients who responded to second-line chemotherapy. **Intervention:** Rituximab maintenance **Comparators:** Observation	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 4%/year (C) and 1,5%/year (O) **Approach:** Markov Model	**Effect:** Mean incremental QALYs were the following: 1.38 (scenario1); 1.37 (scenario2) and 2.11 (scenario3) **Cost:** The mean incremental total cost were: €17,425 (scenario1), €32,668 (scenario2) and €23,736 (scenario3)	**ICER/ICUR:** €11,259/LYG and €12,655/QALY (scenario1); €21,202/LYG and €23,821/QALY (scenario2). €10,591/LYG and €11,245/QALY (scenario3) **Main conclusion:** Although differences in real-world and trial population were found, using real-world data as well as results from long-term trial follow-up showed favourable ICERs for rituximab maintenance. Nevertheless, results showed that caution is required with data synthesis, interpretation and generalisability of results. As different scenarios provide answers to different questions, we recommend healthcare decision-makers to recognise the importance of calculating several cost-effectiveness scenarios.
139	Cost-effectiveness of brentuximab vedotin plus chemotherapy as frontline treatment of stage III or IV classical Hodgkin lymphoma.; Deleea TE.; 2018; United States	**Target Population:** Frontline treatment of stage III or IV classical Hodgkin lymphoma **Intervention:** Brentuximab vedotin + doxorubicin + vinblastine + dacarbazine **Comparators:** Doxorubicin + bleomycin + vinblastine + dacarbazine	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** $100,000/QALY, $150,000/QALY and $200,000/QALY **Cost type: Direct medical costs** **Discount Rates:** 3%/year **Approach:** Semi-Markov Model	**Effect:** Patients receiving A+AVD were estimated to experience 0.90 more discounted LYs and 0.76 more discounted QALYs than patients receiving ABVD. **Cost:** Expected total healthcare costs were $130,706 greater with A+AVD than with ABVD.	**ICER/ICUR:** $172,074/QALY **Main conclusion:** The ICER for A + AVD vs ABVD based on ECHELON-1 is within the range of threshold values for cost-effectiveness in the US. A + AVD is, therefore, likely to be a cost-effective frontline therapy for patients with stage III/IV classical Hodgkin lymphoma from a US healthcare payer perspective.

7.27 **Lymphoma: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
140	Cost-Effectiveness Analysis of Brentuximab Vedotin With Chemotherapy in Newly Diagnosed Stage III and IV Hodgkin Lymphoma.; Huntington SF.; 2018; United States	**Target Population:** Newly Diagnosed Stage III and IV Hodgkin Lymphoma **Intervention:** Brentuximab vedotin + doxorubicin + vinblastine + dacarbazine **Comparators:** Doxorubicin + bleomycin + vinblastine + dacarbazine	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, databases and clinicla trials **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical	**Effect:** AVD+BV was associated with an improvement of 0.56 QALYs compared with treatment with standard ABVD. **Cost:** Incorporating BV into first-line therapy led to significantly higher lifetime health care costs ($361,137 v $184,291)	**ICER/ICUR:** $317,254 per QALY **Main conclusion:** Substituting BV for bleomycin during first-line therapy for stage III or IV HL is unlikely to be cost effective under current drug pricing. Should indication-specific pricing be implemented, significant price reductions for BV used in the first-line setting would be needed to reduce ICERs to more widely acceptable values.
141	Cost-effectiveness analysis of consolidation with brentuximab vedotin for high-risk Hodgkin lymphoma after autologous stem cell transplantation.; Hui L.; 2017; United States	**Target Population:** Risk of Hodgkin lymphoma (HL) progression after autologous stem cell transplantation (ASCT) **Intervention:** Brentuximab vedotin **Comparators:** Active surveillance	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies and database **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical	**Effect:** After quality-of-life adjustments and standard discounting, upfront BV consolidation was associated with an improvement of 1.07 QALYs compared with active surveillance plus BV as salvage **Cost:** However, the strategy of BV consolidation led to significantly higher health care costs ($378,832 vs $219,761)	**ICER/ICUR:** $148,664/QALY **Main conclusion:** BV as consolidation therapy under current US pricing is unlikely to be cost effective at a willingness-to-pay threshold of $100,000 per QALY. However, indication-specific price reductions for the consolidative setting could reduce ICERs to widely acceptable values.
142	Economic evaluation of brentuximab vedotin for persistent Hodgkin lymphoma; Babashov V.; 2017; Canada	**Target Population:** Treatment of relapsed and refractory Hodgkin lymphoma (hl) in the post-autologous stem-cell transplantation **Intervention:** Brentuximab vedotin **Comparators:** Best supportive care	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and clinical trial **WTP threshold:** $100,000/QALY, $150,000/QALY and $200,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Decision Analytical Model	**Effect:** In the base case, treatment with brentuximab vedotin resulted in an incremental 0.544 QALYs per patient **Cost:** In the base case, treatment with brentuximab vedotin resulted in an incremental cost of $89,366 per patient.	**ICER/ICUR:** $164,248/QALY **Main conclusion:** In light of the available information, brentuximab vedotin has an icer exceeding $100,000 per QALY gained, which is a level often classified as having "weak evidence for adoption and appropriate utilization" in Canada. However, it is worth noting that provincial cancer agencies take into account not only the costs and associated icer, but also other factors such as a lack of alternative treatment options and the clinical benefits of expensive cancer drugs. Pricing arrangements should be negotiated, and risk-sharing agreements or patient access schemes should be explored

7.28 **Lymphoma: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
143	Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma post-autologous stem cell transplant: a cost-effectiveness analysis in Scotland.; Parker C.; 2017; Scotland	**Target Population:** Relapsed/refractory Hodgkin lymphoma post-autologous stem cell transplant **Intervention:** Brentuximab vedotin **Comparators:** Chemotherapy with or without radiotherapy (R/C) and C/R with intent to allogeneic hematopoietic stem cell transplantation (alloSCT)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** £50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Partitioned Survival Model	**Effect:** Brentuximab vedotin-treated patients accrued total QALYs of 3.36, yielding incremental QALYs of 1.58 vs C/R and 0.85 vs C/R with the intent to alloSCT. **Cost:** Patients treated with brentuximab vedotin incurred total costs of £88,572, yielding incremental costs of £61,179 vs C/R and –£6,421 vs C/R with intent to alloSCT	**ICER/ICUR:** £38,769/QALY vs C/R whereas C/R with intent to alloSCT was dominated by brentuximab vedotin. **Main conclusion:** Although the base case ICER is above the threshold usually applied in Scotland, it is relatively low compared with other orphan drugs, and lower than the ICER generated using a previous data cut of SG035-0003 that informed a positive recommendation from the Scottish Medicines Consortium, under its decision-making framework for assessment of ultra-orphan medicines.
144	Cost-effectiveness analysis of bortezomib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (VR-CAP) in patients with previously untreated mantle cell lymphoma.; van Keep M.; 2016; United Kingdom	**Target Population:** Patients with previously untreated MCL, for whom haematopoietic stem cell transplantation is unsuitable **Intervention:** bortezomib + rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (VR-CAP) **Comparators:** Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** £20,000 and £30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Markov Model	**Effect:** In the base case, treatment with brentuximab vedotin resulted in an incremental 0.81 QALYs per patient **Cost:** In the base case, treatment with brentuximab vedotin resulted in an incremental cost of £16,212 per patient.	**ICER/ICUR:** £20,043/QALY **Main conclusion:** VR-CAP is a cost-effective option for previously untreated patients with MCL in the UK.
145	Bendamustine-rituximab: a cost-utility analysis in first-line treatment of indolent non-Hodgkin's lymphoma in England and Wales.; Dewilde S.; 2014; England and Wales	**Target Population:** First-line treatment of indolent non-Hodgkin's lymphoma **Intervention:** Bendamustine + Rituximab **Comparators:** Cyclophosphamide + Doxorubicin + Vincristine + Prednisone + Rituximab (CHOP-R) and Cyclophosphamide + Vincristine + Prednisone + Rituximab (CVP-R)	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, Published studies and clinical trials **WTP threshold:** £20,000-£30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** -	**Effect:** In the base case, B-R resulted in an incremental 0.73 QALYs and 0.61 QALYs per patient, with CHOP-R and CVP-R, respectively. **Cost:** In the base case, treatment with brentuximab vedotin resulted in an incremental cost of £3,826 and £4,921 with CHOP-R and CVP-R, respectively.	**ICER/ICUR:** £5,249/QALY (B-R vs CHOP-R) and £8,092/QALY (B-R vs CVP-R) **Main conclusion:** The ICERs for B-R vs CHOP-R and CVP-R were considerably below the thresholds normally regarded as cost-effective in England and Wales

7.29 **Merkel Cell Carcinoma: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
146	Cost Effectiveness of Avelumab for Metastatic Merkel Cell Carcinoma.; Bullement A.; 2019; United Kingdom	**Target Population:** Metastatic Merkel cell carcinoma **Intervention:** Avelumab **Comparators:** Standart Care	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Expert panel, published studies and clinical trials **WTP threshold:** £50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Partitioned Survival Model	**Effect:** An increase of 2.24 and 1.96 QALYs was predicted for avelumab versus SC for the TE and TN populations, respectively. **Cost:** An increase in total cost of £80,646 and £78,981 was predicted for avelumab versus SC for the TE and TN populations, respectively.	**ICER/ICUR:** £35,274/QALY (Treatment Experienced) and £39,178/QALY (Treatment Naive) **Main conclusion:** Avelumab represents a step change in therapy to these patients, and a cost-effective use of NHS resources with a limited budget impact based on an incident population of approximately 100 UK mMCC patients per year.

7.30 **Multiple Myeloma: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
147	Cost-effectiveness of Daratumumab-based Triplet Therapies in Patients With Relapsed or Refractory Multiple Myeloma.; Zhang TT.; 2018; United States	**Target Population:** Patients with relapsed or refractory multiple myeloma (RRMM) **Intervention:** Daratumumab + lenalidomide and dexamethasone (DRd) and Daratumumab + bortezomib and dexamethasone (DVd) **Comparators:** Lenalidomide and dexamethasone (Rd) and Bortezomib and dexamethasone (Vd)	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Semi-Markov Model	**Effect:** Projected incremental gains of 0.263 and 0.370 QALYs for DRd vs Rd and DVd vs Vd, respectively. **Cost:** Projected costs of $359,786 and $105,123 for DRd vs Rd and DVd vs Vd, respectively.	**ICER/ICUR:** $284,180/QALY for DVd compared with Vd and $1,369,062/QALY for DRd compared with Rd **Main conclusion:** Due to the high price of daratumumab, neither the addition of daratumumab to Rd nor Vd proved to be cost-effective under US WTP. However, if the daratumumab price fell to a certain discount level, the DVd regimen might be cost-effective.
148	Cost-effectiveness of Drugs to Treat Relapsed/Refractory Multiple Myeloma in the United States.; Carlson JJ.; 2018; United States	**Target Population:** Treatment for relapsed and/or refractory Multiple Myeloma **Intervention:** carfilzomib (CFZ), elotuzumab (ELO), ixazomib (IX), daratumumab (DAR), and panobinostat (PAN) in combination with lenalidomide (LEN) or bortezomib (BOR)+ dexamethasone (DEX) **Comparators:** Against each other	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database and published studies **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** In the second line, total QALYs ranged from a low of 2.59 for LEN+DEX to a high of 5.44 for DAR+LEN+DEX. Total life years ranged from 3.53 for LEN+DEX to 7.38 for DAR+LEN+DEX. In the third line, results followed a similar pattern, with total QALYs ranging from a low of 2.04 for LEN+DEX to a high of 4.38 for DAR+LEN+DEX. Total life years ranged from 3.25 for LEN+DEX to 6.97 for DAR+LEN+DEX. **Cost:** Total costs ranged from $189,357 for BOR+DEX to $845,527 for DAR+LEN+DEX.Total costs ranged from $175,315 for BOR+DEX to $789,202 for DAR+LEN+DEX.	**ICER/ICUR:** For new second-line regimens versus LEN+DEX were estimated to be $51,000 per QALY for DAR+BOR+DEX, followed by DAR+LEN+DEX ($188,000) and CFZ+LEN+DEX ($211,000), with greater than $400,000 per QALY for ELO+LEN+DEX and IX+LEN+DEX. In the third line, ICERs for new regimens versus LEN+DEX were estimated to range from dominant for PAN+BOR+DEX to $60,000 per QALY for DAR+BOR+DEX, followed by DAR+LEN+DEX ($216,000), CFZ+LEN+DEX ($253,000), and approximately $500,000 per QALY for ELO+LEN+DEX and IX+LEN+DEX. **Main conclusion:** Only the addition of DAR or PAN may be considered cost-effective options according to commonly cited thresholds, and PAN+BOR+DEX results require cautious interpretation. Achieving levels of value more closely aligned with patient benefit would require substantial discounts from the remaining
149	Cost-effectiveness of Pomalidomide, Carfilzomib, and Daratumumab for the Treatment of Patients with Heavily Pretreated Relapsed-refractory Multiple Myeloma in the United States.; Pelligra CG.; 2017; United States	**Target Population:** Patients with heavily pretreated relapsed-refractory multiple myeloma (RRMM) **Intervention:** Daratumumab and Carfilzomib **Comparators:** Pomalidomide	**Perspective:** Payer **Time Horizon:** 3 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $50,000/QALY and $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** State Trasition Model	**Effect:** The use of POM-d was associated with similar life-years and quality-adjusted life-years gained compared with DARA and CAR (incremental: life-years, +0.02 and +0.07, respectively; quality-adjusted life-years, +0.01 and +0.05). **Cost:**With a cost less than that of DARA (-$8,919) and similar to that of CAR (-$195).	**ICER/ICUR:** An equal efficacy scenario resulted in cost-savings relative to those of both DARA and CAR (-$11,779 and -$12,595). **Main conclusion:** POM-d may be a cost-effective treatment option relative to DARA or CAR in heavily pretreated patients with RRMM in the US.

7.31 **Non Small Cell Lung cancer: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
150	Cost-effectiveness of second-line atezolizumab in Canada for advanced non-small cell lung cancer (NSCLC); Ondhia U.; 2019; Canada	**Target Population:** Advanced NSCLC after first-line platinum-doublet chemotherapy **Intervention:** Atezolizumab **Comparators:** Docetaxel and Nivolumab	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Expert panel, published studies and clinical trials **WTP threshold:** $125,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 1.5%/year **Approach:** Partitioned Survival Model	**Effect:** Atezolizumab demonstrated a quality-adjusted life-year (QALY) gain of 0.60 compared with docetaxel. Atezolizumab dominated nivolumab (regardless of dosing regimen), based on modest differences in both QALYs and costs. **Cost:** An incremental cost of $85,073, compared with docetaxel.	**ICER/ICUR:** $142,074/QALY (vs Docetaxel), Dominated vs Nivolumab **Main conclusion:** Atezolizumab represents a cost-effective therapeutic option in Canada for the treatment of patients with advanced NSCLC who progress after first-line platinum doublet chemotherapy.
151	Cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US.; Insinga RP.; 2019; United States	**Target Population:** Metastatic, Squamous, non-small-cell lung cancer (NSCLC) patients **Intervention:** Pembrolizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** Overall, P + C is projected to increase life expectancy by 1.95 years vs. C (3.86 versus 1.91).The discounted QALY gain with pembrolizumab plus chemotherapy is 1.38 QALYs. **Cost:** Incremental discounted costs associated with use of pembrolizumab plus chemotherapy versus chemotherapy are $119,451	**ICER/ICUR:** $86,293/QALY; (PD-L1 ≥ 50%) = $99,777/QALY; (PD-L1 ≥ 1-49%) = $85,986/QALY; ICER (<1%) = $87,507/QALY **Main conclusion:** Overall, and within all relevant PD-L1 subgroups, use of P + C yields an ICER below $100,000/QALY, and can be a cost-effective first-line treatment for eligible metastatic squamous NSCLC patients for whom chemotherapy is currently administered. In the PD-L1 ≥ 50% subgroup, additional follow-up within trials of pembrolizumab plus chemotherapy and pembrolizumab monotherapy are needed to better define cost-effectiveness between these comparators.
152	Cost-effectiveness analysis of first-line pembrolizumab treatment for PD-L1 positive, non-small cell lung cancer in China.; Liao W.; 2019; China	**Target Population:** Advanced NSCLC patients with PD-L1 positive cancer **Intervention:** Pembrolizumab **Comparators:** Chemotherapy	**Perspective:** Societal **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $26,481/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Pembrolizumab gained 0.45 QALYs compared to chemotherapy. **Cost:** Pembrolizumab yielded an incremental cost of $46,362 per patient compared to chemotherapy.	**ICER/ICUR:** $103,128/QALY **Main conclusion:** Not likely to be cost-effective in the treatment of PD-L1 positive, NSCLC for Chinese patients
153	Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (>50%) metastatic squamous and non-squamous non-small cell lung cancer in France.; Chouaid C.; 2019; France	**Target Population:** Metastatic Non-Small-Cell Lung Cancer (NSCLC) patients with no EGFR mutations or ALK translocations **Intervention:** Pembrolizumab **Comparators:** Standart care platinum based chemotherapy	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Clinical trials and published studies **WTP threshold:** €100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 4%/year **Approach:** Partitioned Survival Model	**Effect:** For squamous NSCLC, pembrolizumab was projected to increase life expectancy of patients by 0.93 LY (11 months), and 0.74 QALY (9 months). **Cost:** An incremental cost of €62,032 compared with platinum-based doublets was estimated.	**ICER/ICUR:** (vs platinum-based doublets) = €66,825/LY and €84,097/QALY ; (vs platinum-based chemotherapy with paclitaxel plus bevacizumab)= €62,846/LY and €78,729/QALY; Dominated against remgimens including pemetrexed **Main conclusion:** Pembrolizumab appears cost-effective versus SoC chemotherapy for first-line treatment of PD-L1-positive (50%) metastatic NSCLC patients in France, assuming willingness-to-pay under 100,000€/QALY
154	Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer in the Context of the US Health Care System.; Criss SD.; 2018; United States	**Target Population:** After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer **Intervention:** Durvalumab consolidation therapy until progression or for a maximum of 1 year **Comparators:** No consolidation therapy until progression	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Database, Published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Decision Analytical Model	**Effect:** No consolidation therapy after chemoradiotherapy resulted in a mean quality-adjusted survival per patient of 2.34QALYs. Durvalumab consolidation therapy resulted in a mean quality-adjusted survival per patient of 2.57 QALYs **Cost:** No consolidation therapy after chemoradiotherapy resulted in a mean cost per patient of $185,944 and Durvalumab consolidation therapy resulted in a mean cost per patient of $201,563.	**ICER/ICUR:** $67,421 **Main conclusion:** Durvalumab consolidation therapy represents an indication where expensive immunotherapies can be cost-effective. Treating with immunotherapy earlier in the course of cancer progression can provide significant value, despite having a substantial budgetary consequence.

7.32 **Non Small Cell Lung cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
155	Modelled Economic Evaluation of Nivolumab for the Treatment of Second-Line Advanced or Metastatic Squamous Non-Small-Cell Lung Cancer in Australia Using Both Partition Survival and Markov Models.; Gao L.; 2018; Australia	**Target Population:** Patients with advanced or metastatic squamous non-small-cell lung cancer (NSCLC) **Intervention:** Nivolumab **Comparators:** Docetaxel	**Perspective:** Payer **Time Horizon:** 6 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** AUS $50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model and Partitioned Survival Model	**Effect:** In the Partitioned Survival Model,with higher costs (A$137,935), QALYs (1.06) and LYs (1.51), while patients who received docetaxel treatment had lower costs (A$119,257), QALYs (0.46) and LYs (0.86). In the Markov Model, nivolumab had the following results: QALY (1.03 vs. 0.68) and LYs (1.32 vs. 0.91) when compared to docetaxel. **Cost:** In the Partitioned Survival Model, nivolumab had higher costs (A$137,935), , while patients who received docetaxel treatment had lower costs (A$119,257).In the Markov Model, nivolumab was again associated with higher cost (A$100,236 vs. A$22,534) when compared to docetaxel.	**ICER/ICUR:** With Partitioned Survival Model = A$198,862/QALY and A$181,623/LY and for Markov Model = A$220,029/QALY and A$193,459/LY **Main conclusion:** Using an often-quoted willingness-to-pay per QALY threshold in Australia (i.e. A$50,000), the treatment with nivolumab cannot be considered cost-effective. It might be funded publicly by special arrangements given unmet clinical needs for patients.
156	A Trial-Based Cost-Effectiveness Analysis of Bevacizumab and Chemotherapy versus Chemotherapy Alone for Advanced Nonsquamous Non-Small-Cell Lung Cancer in China.; Li X.; 2018; China	**Target Population:** First-line treatment of advanced nonsquamous NSCLC **Intervention:** Bevacizumab + Carboplatin + Paclitaxel **Comparators:** Carboplatin + Paclitaxel	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, clinical trials and published studies **WTP threshold:** $24,314/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** QALYs were 1.17 years in the B+CP group and 0.83 years in the P+CP group, resulting in a difference of 0.34 years. **Cost:** -	**ICER/ICUR:** $130,937.09/QALY **Main conclusion:** Bevacizumab is not cost-effective when combined with chemotherapy for patients with advanced nonsquamous NSCLC based on the Chinese health care system, resulting in a less demand in the Chinese market.
157	Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US.; Insinga RP.; 2018; United States	**Target Population:** Metastatic, non-squamous, NSCLC patients **Intervention:** Pembrolizumab + Chemotherapy (carboplatin/cisplatin + pemetrexed) **Comparators:** Chemotherapy (carboplatin/cisplatin + pemetrexed)	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Database, clinical trials and published studies **WTP threshold:** $180,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** First line use of pembrolizumab plus chemotherapy in metastatic non-squamous NSCLC patients is projected to increase discounted life expectancy by 1.73 years vs. trial chemotherapy (3.51 years versus 1.78 years) **Cost:** incremental discounted costs associated with use of pembrolizumab plus chemotherapy versus chemotherapy are $150,888	**ICER/ICUR:** $52,000/QALY in the UK and $49,000/QALY in the US **Main conclusion:** Evidence suggests first-line pembrolizumab for NSCLC may be cost-effective in the US but not the UK, in spite of very similar ICER values in both countries.
158	Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer.; Gerogieva M.; 2018; United States and United Kingdom	**Target Population:** Advanced NSCLC patients with PD-L1 expression ≥50%, non-mutated EGFR, and non-translocated ALK **Intervention:** Pembrolizumab **Comparators:** Platinum-doublet chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Published studies and clinical trials **WTP threshold:** UK was $42,000/QALY and US was $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Patients treated with pembrolizumab accumulated 1.80 QALYs, for moderate dependency between outcomes, compared to 1.06 QALYs with chemotherapy. **Cost:** -	**ICER/ICUR:** $49,000/QALY in the UK and $52,000/QALY in the US **Main conclusion:** Evidence suggests first-line pembrolizumab for NSCLC may be cost-effective in the US but not the UK, in spite of very similar ICER values in both countries.
159	First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective; Hu X.; 2018; United Kingdom	**Target Population:** First-line treatment for patients with PD-L1 positive NSCLC **Intervention:** Pembrolizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** £50,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Markov Model	**Effect:** In the base case, pembrolizumab is projected to increase patient's life expectancy by 1.32 life-years over chemotherapy (2.45 vs. 1.13) and 0.83 QALYs (1.55 vs. 0.71). **Cost:** In the base case, pembrolizumab is projected to have an additional cost of £72,465 cost compared to chemotherapy only	**ICER/ICUR:** In the full non-squamous population, ICERs are $104,823/QALY and $87,242/LY, for PD-L1 subgroups are $103,402/QALY, $66,837/QALY, and $183,529/QALY for PD-L1 ≥ 50%, 1-49% and <1% groups **Main conclusion:** The addition of pembrolizumab to chemotherapy is projected to extend life expectancy to a point not previously seen in previously untreated metastatic non-squamous NSCLC. Although ICERs vary by sub-group and comparator, results suggest pembrolizumab + chemotherapy yields ICERs near, or in most cases, well below a 3-times US per capita GDP threshold of $180,000/QALY, and may be a cost-effective first-line treatment for metastatic non-squamous NSCLC patients. **ICER/ICUR:** £86,913/QALY **Main conclusion:** Using a willingness-to-pay threshold of £50,000, pembrolizumab is not cost-effective at its current list price and a discount of 50% or more is required for it to be cost-effective comparing to commonly prescribed chemotherapy. Risk-sharing contracts may be helpful in resolving some of the underlying uncertainty associated with the long-term survival and varying extent of patient response.

7.33 **Non Small Cell Lung cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
160	An exploratory case study of the impact of expanding cost-effectiveness analysis for second-line nivolumab for patients with squamous non-small cell lung cancer in Canada: Does it make a difference?; Shafrin J.; 2018; Canada	**Target Population:** Second-line treatment of patients with squamous non-small cell lung cancer (NSCLC) **Intervention:** Nivolumab **Comparators:** Docetaxel	**Perspective:** Payer and Societal **Time Horizon:** 10 years **Parameter Sources:** Published studies, clinical trials and database **WTP threshold:** CAD $150,000/QALY **Cost type:** Net monetary benefit **Discount Rates:** 5%/year **Approach:** Partitioned Survival Model	**Effect:** Patients treated with nivolumab gained 0.66 more QALYs and 0.82 more life years per person than those treated with docetaxel. **Cost:** Total costs of nivolumab were $100,168 CAD higher than docetaxel, largely due to higher treatment acquisition costs (+$90,297 CAD)	**ICER/ICUR:** $151,560, $141,344, and $80,645 CAD per QALY from the traditional payer, traditional societal, and broad societal perspectives, respectively. **Main conclusion:** The adopted perspective significantly impacted estimates of nivolumab's cost-effectiveness. In our case study, about half of nivolumab's incremental benefit in advanced squamous NSCLC was omitted using a traditional payer perspective. This analysis suggests the need to broaden cost-effectiveness beyond the traditional payer perspective in order to ensure that all treatment benefits and costs to society are captured
161	Cost-effectiveness analysis of the addition of bevacizumab to chemotherapy as induction and maintenance therapy for metastatic non-squamous non-small-cell lung cancer.; Zheng H.; 2018; China	**Target Population:** Patients with metastatic non-squamous non-small-cell lung cancer (NSCLC) **Intervention:** Bevacizumab + Paclitaxel + Carboplatin **Comparators:** Paclitaxel + Carboplatin	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $23,970/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** The B + PC treatment was more more effective (1.07 QALYs versus 0.80 QALYs) compared with the PC treatment. **Cost:** The B + PC treatment was more costly ($112,943.40 versus $32,171.43).	**ICER/ICUR:** $299,155.44/QALY **Main conclusion:** The addition of B to first-line PC induction and maintenance therapy was not determined to be a cost-effective strategy for metastatic non-squamous NSCLC in China, even when an assistance program was provided.
162	The effect of PD-L1 testing on the cost-effectiveness and economic impact of immune checkpoint inhibitors for the second-line treatment of NSCLC; Aguiar PN. Jr.; 2017; United States	**Target Population:** Second-line treatment of NSCLC **Intervention:** Nivolumab, Pembrolizumab and Atezolizumab **Comparators:** Docetaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Decision Analytical Model	**Effect:** The incremental quality-adjusted life year (QALY) for nivolumab was 0.417 among squamous tumors and 0.287 among non-squamous tumors. The QALY gain in the base case for atezolizumab was 0.354. Compared with treating all patients, the selection of patients by PD-L1 expression improved incremental QALY by up to 183% and decreased the ICER by up to 65%. Pembrolizumab was studied only in patients whose tumors expressed PD-L1. The QALY gain was 0.346. **Cost:** Total costs with the strategies were the following: $104,453 (nivo; squamous), $100,791 (nivo; non squamous), $82,201 (pembro) and $122,155 (atezo)	**ICER/ICUR:**(nivo ; Squamous) = $155 605/QALY; (nivo ; non-Squamous) = $187 685/QALY; (atezo) = $215 802/QALY; (pembro) = $98 421/QALY **Main conclusion:** The use of PD-L1 expression as a biomarker increases cost-effectiveness of immunotherapy but also diminishes the number of potential life-years saved.
163	Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States.; Huang M.; 2017; United States	**Target Population:** Patients aged ≥18 years with stage IV NSCLC, TPS ≥50%, without epidermal growth factor receptor (EGFR)-activating mutations or anaplastic lymphoma kinase (ALK) translocations who received no prior systemic chemotherapy **Intervention:** Pembrolizumab **Comparators:** Standard-of-care (SoC) platinum-based chemotherapy	**Perspective:** Payer **Time Horizon:** 20 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY and $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** In the base-case scenario, pembrolizumab resulted in an expected gain of 1.31 life-years (LYs) and 1.05 QALYs. **Cost:** In the base-case scenario, pembrolizumab resulted in an incremental cost of $102,439 compared with SoC.	**ICER/ICUR:** $97,621/QALY and $78,344/LY. **Main conclusion:** Pembrolizumab is projected to be a cost-effective option compared with SoC platinum-based chemotherapy as first-line treatment in adults with metastatic NSCLC expressing high levels of PD-L1.
164	Cost-effectiveness of pemetrexed in combination with cisplatin as first line treatment for patients with advanced non-squamous non-small-cell lung cancer in Spain.; González García J.; 2017; Spain	**Target Population:** Patients with advanced non-squamous non-small-cell lung **Intervention:** Bevacizumab + cisplatin + gemcitabine and Bevacizumab + carboplatin + paclitaxel **Comparators:** Cisplatin + pemetrexed	**Perspective:** - **Time Horizon:** 1 year **Parameter Sources:** Database, clinical trials and published studies **WTP threshold:** - **Cost type:** Direct cost of drugs **Discount Rates:** 0%/year **Approach:** Decision Analytical Model	**Effect:** The PFS obtained in clinical trials with cis/pem, cis/gem/bev and carb/pac/bev was: 6.9, 6.7 and 6.2 months, respectively. **Cost:** The mean cost of treatment per patient for the gem/cis/bev, cis/pem, and carb/pac/bev treatment regimens would be 15,594.74€, 19,442.01€ and 36,095.17€ respectively.	**ICER/ICUR:** The car/pac/bev regimen is the dominated alternative. The incremental cost-effectiveness ratio per month of additional PFS between cis/pem and cis/gem/bev was €19 303. **Main conclusion:** Estimating a 30% reduction in acquisition costs for pemetrexed (Alimta ®Eli Lilly Nederland B.V.), due to the forthcoming launch of generic medications, the cis/pem treatment would become the predominant alternative for 1st line treatment of NSCLC patients, by offering the best health results at a lower cost.

7.34 **Non Small Cell Lung cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
165	A Cost-Effectiveness Analysis of Nivolumab versus Docetaxel for Advanced Nonsquamous NSCLC Including PD-L1 Testing.; Matter-Walstra K.; 2016; Switzerland	**Target Population:** Advanced Nonsquamous NSCLC **Intervention:** Nivolumab **Comparators:** Docetaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** CHF100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Markov Model	**Effect:** In the base case model, NIV had mean 0.69 QALYs compared with DOC mean 0.53 QALYs per patient **Cost:** In the base case model, NIV had a mean cost of CHF66,208 per patient while DOC had a mean cost of CHF37,618 per patient.	**ICER/ICUR:** CHF177,478/QALY and for (PD-L1+) = CHF124,891/QALY **Main conclusion:** Compared with DOC, NIV is not cost-effective for the treatment of nonsquamous NSCLC at current prices in the Swiss health care setting. Price reduction or PD-L1 testing and selection of patients for NIV on the basis of test positivity improves cost-effectiveness compared with DOC.
166	Cost-effectiveness of pembrolizumab versus docetaxel for the treatment of previously treated PD-L1 positive advanced NSCLC patients in the United States.; Huang M.; 2017; United States	**Target Population:** Previously treated advanced non-squamous cell lung cancer (NSCLC) with PD-L1 positive tumors (total proportion score [TPS] ≥ 50%) **Intervention:** Pembrolizumab **Comparators:** Docetaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $200,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** Base case results project for PD-L1 positive (TPS ≥50%) patients treated with pembrolizumab a mean survival of 2.25 years. For docetaxel, a mean survival time of 1.07 years was estimated. Expected QALYs were 1.71 and 0.76 for pembrolizumab and docetaxel, respectively. **Cost:** Base-case results show a difference of $160,522 in the total average per-patient direct cost of treatment with pembrolizumab ($297,443) vs. docetaxel ($136,921)	**ICER/ICUR:** $168,619/QALY **Main conclusion:** Pembrolizumab improves survival, increases QALYs, and can be considered as a cost-effective option compared to docetaxel in PD-L1 positive (TPS ≥50%) pre-treated advanced NSCLC patients in the US.
167	Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes.; Goeree R.; 2016; Canada	**Target Population:** Patients with advanced squamous non-small cell lung cancer (NSCLC) who were previously treated **Intervention:** Nivolumab **Comparators:** Docetaxel and Erlotinib	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies, expert panel and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model and Partitioned Survival Model	**Effect:** Regarding the PS model: Nivolumab was found to result in an increased life expectancy (discounted) of 0.82 and 0.93 years, and an increased QALYs of 0.66 and 0.70 when compared to docetaxel and erlotinib, respectively. Regarding the Markov model it was found that patients treated with nivolumab had an increased discounted life expectancy of 0.82 and 0.92 years, and an increased QALYs of 0.66 and 0.70 when compared to docetaxel and erlotinib, respectively. **Cost:** Regarding the PS model: Nivolumab was found to result in an increased per patient cost of $100,168 and $99,084, when compared to docetaxel and erlotinib, respectively. Regarding the Markov model, it was found that patients treated with nivolumab resulted in an increased per patient cost of $100,204 and $99,096, when compared to docetaxel and erlotinib, respectively.	**ICER/ICUR:** PS model: $151,560/QALY) vs DOC) and $140,601/QALY (vs ERL) Markov Model: $152,229/QALY (vs DOC) and $141,838/QALY (vs ERL) **Main conclusion:** Nivolumab was found to involve a trade-off between improved patient survival and QALYs, and increased cost. It was found that the use of a PS or Markov model produced very similar estimates of expected cost, outcomes, and incremental cost-utility.
168	Cost-effectiveness of first-line induction and maintenance treatment sequences in non-squamous non-small cell lung cancer (NSCLC) in the U.S.; Kumar G.; 2015; United States	**Target Population:** Advanced non-squamous NSCLC **Intervention:** Bevacizumab + Carboplatin + Paclitaxel **Comparators:** Gemcitabine + Cisplatin	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 3.5%/year **Approach:** Decision Analytical Model	**Effect:** **Cost:** The base case results found overall costs ranged from $62,620 for cisplatin + gemcitabine followed by (→) BSC, to $135,488 for bevacizumab, carboplatin and paclitaxel → bevacizumab maintenance	**ICER/ICUR:** Dominated **Main conclusion:** Depending on the specific cost-effectiveness threshold used by a decision maker, the most cost-effective treatment sequence may include the referent comparator gemcitabine + cisplatin and the studied regimens of gemcitabine + cisplatin → erlotinib, pemetrexed + cisplatin → pemetrexed.

7.35 **Ovarian cancer Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
169	First- and second-line bevacizumab in ovarian cancer: A Belgian cost-utility analysis; Neyt M.; 2018; Belgium	**Target Population:** Treatment of recurrent ovarian cancer (platinum-sensitive or platinum-resistant) **Intervention:** 1st line : Bevacizumab + chemotherapy and 2nd line: Bevacizumab **Comparators:** Standard chemotherapy alone	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** - **Cost type:** Direct medical costs **Discount Rates:** 3%/year (C) and 1,5%/year (O) **Approach:** Markov Model	**Effect:** The incremental life years and the incrementental QALYs gained in the different clinical trials considered varied between 0.13-1.07 and 0.06-0.77, respectively. **Cost:** The incremental costs across all clinical trials varied between €27,188-€56,897.	**ICER/ICUR:** First-line bevacizumab are on average €158,000/QALY (GOG-0218 trial) and €443,000/QALY (ICON7 trial)	For second-line bevacizumab, ICERs are on average €587,000/QALY (OCEANS trial) and €172,000/QALY (AURELIA trial) **Main conclusion:** From a health economic perspective, ICERs of bevacizumab are relatively high. The most favourable results are found for first-line treatment of stage IV ovarian cancer patients. Price reductions have a major impact on the estimated ICERs. It is recommended to take these findings into account when re-evaluating the reimbursement of bevacizumab in ovarian cancer
170	Economic Evaluation of Bevacizumab for Treatment of Platinum-Resistant Recurrent Ovarian Cancer in Canada; Ball G.; 2018; Canada	**Target Population:** Treatment of Platinum-Resistant Recurrent Ovarian Cancer **Intervention:** Bevacizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** 7 years **Parameter Sources:** Published studies and clinical trials **WTP threshold:** CAD$100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Partitioned Survival Model	**Effect:** Total estimated quality-adjusted life-years (QALYs) were 1.1055 and 0.9926 for the BEV and chemotherapy arms, respectively. **Cost:** Total costs for the BEV and chemotherapy treatment arms were CAD$79,086 and CAD$54,982, respectively.	**ICER/ICUR:** CAD$213,424 per QALY	**Main conclusion:** The results of our analysis suggest that the addition of bevacizumab to single-agent chemotherapy treatment, while improving patient outcomes, is unlikely to be cost-effective in this Canadian patient population.
171	Adding bevacizumab to single agent chemotherapy for the treatment of platinum-resistant recurrent ovarian cancer: A cost effectiveness analysis of the AURELIA trial; Wysham WZ.; 2017; United States	**Target Population:** Treatment of platinum-resistant recurrent ovarian cancer **Intervention:** Bevacizumab + Single agent chemotherapy **Comparators:** Single agent chemotherapy	**Perspective:** Payer **Time Horizon:** 15 months **Parameter Sources:** Published studies and clinical trials **WTP threshold:** $50,000/QALY and $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Decision Analytical	**Effect:** - **Cost:** -	**ICER/ICUR:** $285,624/QALY and $151,059/PFSLY	**Main conclusion:** Despite gains in QALY and PFS, the addition of B to single agent CT for treatment of platinum-resistant recurrent ovarian cancer is not cost effective. Benefits, risks, and costs associated with treatment should be taken into consideration when prescribing chemotherapy for this patient population.
172	The cost-effectiveness of bevacizumab for the treatment of advanced ovarian cancer in Canada; Duong M.; 2016; Canada	**Target Population:** Ovarian cancer patients with a high risk of progression (stage iii suboptimally debulked, and stage iii or iv with unresectable disease) **Intervention:** Bevacizumab + standard chemotherapy **Comparators:** Standard chemotherapy	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 5%/year **Approach:** Markov Model	**Effect:** Ovarian cancer patients at high risk of progression receiving bevacizumab plus standard chemotherapy experienced a mean incremental QALY's gain of 0.374 years. **Cost:** The addition of bevacizumab to standart chemotherapy had an additional cost of $35,901.54 per patient.	**ICER/ICUR:** $95,942/QALY	**Main conclusion:** Bevacizumab in addition to chemotherapy is a cost-effective alternative for ovarian cancer patients who are at high risk of progression (stage iii suboptimally debulked, and stage iii or iv with unresectable disease). Using the $100,000 per qaly threshold in a probabilistic sensitivity analysis, it was determined that, compared with standard chemotherapy, the addition of bevacizumab to chemotherapy is cost-effective in 56% of tested scenarios.
173	The Cost-Effectiveness of Bevacizumab in Advanced Ovarian Cancer Using Evidence from the ICON7 Trial.; Hinde S.; 2016; United Kingdom	**Target Population:** Advanced ovarian cancer **Intervention:** Bevacizumab + Carboplatin + Paclitaxel **Comparators:** Carboplatin + Paclitaxel	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Clinical trials, published studies and database **WTP threshold:** £20,000/QALY and £30,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Partitioned Survival Model	**Effect:** In the base-case analysis, bevacizumab is associated with a larger total number of QALYs than chemotherapy only (incremental QALYs 0.381). **Cost:** In the base-case analysis, the bevacizumab arm was associated with higher costs than chemotherapy alone (incremental costs £18,684).	**ICER/ICUR:** £48,975/QALY	**Main conclusion:** The lower dose of bevacizumab for advanced ovarian cancer is not cost-effective based on the product's list price and using NICE's cost-effectiveness thresholds. Significant price discounts would be needed to make the drug affordable to the NHS.

7.36 **Ovarian cancer: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
174	Is FDA-Approved Bevacizumab Cost-Effective When Included in the Treatment of Platinum-Resistant Recurrent Ovarian Cancer?; Chappell NP.; 2016; United States	**Target Population:** Treatment of Platinum-Resistant Recurrent Ovarian Cancer **Intervention:** Bevacizumab + Chemotherapy **Comparators:** Chemotherapy	**Perspective:** Payer **Time Horizon:** - **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Decision Analytical	**Effect:** The CHEMO arm, least effective in AURELIA with a median PFS of 3.4 months .The CHEMO plus BEV arm had an average PFS of 6.7 months. **Cost:** The CHEMO arm, was the least costly arm, with an average regimen cost of $21,611. The CHEMO plus BEV arm had an average regimen cost of $66,511 per patient.	**ICER/ICUR:** $160,000/QALY **Main conclusion:** Using a willingness-to-pay threshold of $100,000 ICER, the addition of BEV to chemotherapy either demonstrates or approaches cost-effectiveness and NHB when added to the treatment of patients with PROC.
175	A cost-utility analysis of NRG Oncology/Gynecologic Oncology Group Protocol 218: incorporating prospectively collected quality-of-life scores in an economic model of treatment of ovarian cancer.; Cohn DE.; 2015; United States	**Target Population:** Primary treatment of advanced-stage epithelial ovarian cancer **Intervention:** Bevacizumab + Paclitaxel + Carboplatin (PCB) and PCB + Bevacizumab maintenance (PCB+B) **Comparators:** Paclitaxel + Carboplatin (PC)	**Perspective:** Payer **Time Horizon:** 5 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $150,000/QAPFY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** PC was the least effective (mean 1.1 quality-adjusted progression-free years [QA-PFY]) regimen. PCB yelded 1.13 QA-PFY and PCB+B, 1.25 QA-PFY. **Cost:** PC was the least expensive $4,044 regimen. PCB had a cost of $43,703 and PCB+B with a total cost of $122,700 was the most expensive regimen	**ICER/ICUR:** PCB was $792,380/QA-PFY and PCB+B was $632,571/PFY **Main conclusion:** In this cost-utility model, incorporation of QOL into an analysis of GOG 218 led to less favorable ICER (by >$150,000/QA-PFY) in regimens containing B compared with those that do not include B.
176	Bevacizumab in treatment of high-risk ovarian cancer--a cost-effectiveness analysis.; Chan JK.; 2014; United States	**Target Population:** High-risk advanced ovarian cancer patients with survival benefit. **Intervention:** Bevacizumab + Paclitaxel + Carboplatin + maintenance **Comparators:** Paclitaxel + Cabroplatin (PC) Bevacizumab)PCB + mB)	**Perspective:** Payer **Time Horizon:** 3,8 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $200,000/LY **Cost type:** Direct medical costs **Discount Rates:** - **Approach:** Markov Model	**Effect:** The median progression-free survival after combination chemotherapy was 10.5 months, and the addition of B improved this by an additional 5.4 months . Moreover, the addition of B improved the median overall survival by nearly 8 months (28.8 months vs. 36.6 months). **Cost:** -	**ICER/ICUR:** $167,771/LY **Main conclusion:** In this clinically relevant subset of women with high-risk advanced ovarian cancer with overall survival benefit after bevacizumab, our economic model suggests that the incremental cost of bevacizumab was approximately $170,000.
177	Cost-effectiveness of adding bevacizumab to first line therapy for patients with advanced ovarian cancer.; Mehta DA.; 2014; United States	**Target Population:** First line treatment for patients with advanced ovarian cancer **Intervention:** Bevacizumab + Paclitaxel + Carboplatin **Comparators:** Paclitaxel + Carboplatin	**Perspective:** Societal **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** - **Cost:** -	**ICER/ICUR:** GOG-218: $2,420,691/QALY, ICON-7: $225,515/QALY + for stage IV patients ($126,169/QALY), ECOG PS1 patients ($116,575/QALY) and for patients with suboptimal residual disease ($122,822/QALY) as per the ICON-7 protocol **Main conclusion:** Addition of bevacizumab, by in large, is cost-ineffective. It can become cost-effective with the ICON-7 protocol, in patients at high risk of progression using biosimilar bevacizumab.

7.37 **Pleural Mesothelioma: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
178	Cost-effectiveness analysis of additional bevacizumab to pemetrexed plus cisplatin for malignant pleural mesothelioma based on the MAPS trial; Zhan M.; 2017; China	**Target Population:** Patients with unresectable Malignant Pleural Mesothelioma **Intervention:** Bevacizumab + Pemetrexed + Cisplatin **Comparators:** Pemetrexed + Cisplatin	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Published studies, database and clinical trials **WTP threshold:** $23,970/QALY **Cost type:** Direct medical costs **Discount Rates:** 0%/year **Approach:** Markov Model	**Effect:** The addition of bevacizumab to PC was estimated to gain of 0.112 QALYs per patient, compared to pemetrexed combined with cisplatin. **Cost:** The addition of bevacizumab to PC was estimated to increase the cost by $81446.69, compared to pemetrexed combined with cisplatin.	**ICER/ICUR:** $727,202.589 per QALY **Main conclusion:** The combination of bevacizumab with PC chemotherapy is not a cost-effective treatment option for MPM in China. Given its positive clinical value and extremely low incidence of MPM, an appropriate price discount, assistance programs and medical insurance should be considered to make bevacizumab more affordable for this rare patient population.

7.38 **Renal Cell carcinoma: Summary of the studies**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
179	A Cost-Effectiveness Analysis of Nivolumab and Ipilimumab Versus Sunitinib in First-Line Intermediate- to Poor-Risk Advanced Renal Cell Carcinoma; Reinhorn D.; 2019; United States	**Target Population:** First-line treatment of intermediate- to poor-risk advanced Renal Cell Carcinoma **Intervention:** Nivolumab + Ipilimumab **Comparators:** Sunitinib	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Nivolumab and ipilimumab generated a gain of 0.978 QALYs over sunitinib. **Cost:** The total mean cost per-patient of nivolumab and ipilimumab versus sunitinib was $292,308 and $169,287, respectfully.	**ICER/ICUR:** $125,739/QALY **Main conclusion:** Our analysis established that the base case ICER in the model for nivolumab and ipilimumab versus sunitinib is below what some would consider the upper limit of the theoretical willingness-to-pay threshold in the U.S. ($150,000/QALY) and is thus estimated to be cost-effective.
180	Cost-effectiveness of nivolumab plus ipilimumab as first-line therapy in advanced renal-cell carcinoma; Wu B.; 2018; United States, United Kingdom and China	**Target Population:** First-line treatment of advanced RCC **Intervention:** Nivolumab + Ipilimumab **Comparators:** Sunitinib	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Databases, published studies and clinical trials **WTP threshold:** $150,000/QALY (US), $65,000/QALY (UK) and $27,351/QALY (China) **Cost type:** Direct medical costs **Discount Rates:** 3%/year (US), 3.5%/year (UK) and 5%/year (China) **Approach:** Decision Analytical	**Effect:** Compared with the sunitinib strategy, the mean incremental QALYs of the nivolumab plus ipilimumab were 0.76, 0.75 and 0.70 for the population in the US, UK and China, respectively. **Cost:** Compared with the sunitinib strategy, the mean incremental costs of the nivolumab plus ipilimumab were $65,114, $94,356 and $3,286 for the population in the US, UK and China, respectively.	**ICER/ICUR:** In the US was $85,506/QALY, in the UK was $126,499/QALY and in China $4,682/QALY **Main conclusion:** Nivolumab plus ipilimumab as first-line treatment could gain more health benefits for advanced RCC in comparison with standard sunitinib, which is considered to be cost-effective in the US and China but not in the UK.
181	Nivolumab in the Treatment of Metastatic Renal Cell Carcinoma: A Cost-Utility Analysis; Raphael J.; 2018; Canada	**Target Population:** Patients with metastatic renal cell carcinoma (mRCC) **Intervention:** Nivolumab **Comparators:** Everolimus	**Perspective:** Payer **Time Horizon:** Payer **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $4,167/QALM **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Compared with everolimus, nivolumab provided an additional 4.2 QALM. **Cost:** Compared with everolimus, nivolumab had an incremental cost of $34,153 per patient.	**ICER/ICUR:** $8,138/QALM **Main conclusion:** Compared with everolimus, nivolumab is unlikely to be cost-effective for the treatment of mRCC from a Canadian health care perspective with its current price assuming a WTP of $50,000/QALY. Although mRCC patients derive a meaningful clinical benefit from nivolumab, considerations should be given to avoid drug wastage and increase the WTP threshold to render this strategy more affordable.

7.39 **Renal Cell carcinoma: Summary of the studies (cont.)**

Reference Number	Title, Author, Year, Country	Population and Comparison	Study details	Results	Conclusions
182	Cost-effectiveness comparison of cabozantinib with everolimus, axitinib, and nivolumab in the treatment of advanced renal cell carcinoma following the failure of prior therapy in England.; Meng J.; 2018; England	**Target Population:** Adult patients with advanced renal cell carcinoma (aRCC) **Intervention:** Cabozantinib **Comparators:** Everolimus, Axitinib and Nivolumab	**Perspective:** Payer and Societal **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** £100,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3,5%/year **Approach:** Partitioned Survival Model	**Effect:** Cabozantinib was more effective than nivolumab, the QALY difference was 0.18 in favour of the cavozantinib approach. **Cost:** Cabozantinib was less costly than nivolumab, the incremental cost was -£6,742 GBP.	**ICER/ICUR:** Versus axitinib and everolimus were £98,967/QALY and £137,450/QALY, respectively. Cabozantinib was less costly and more effective than nivolumab **Main conclusion:** Treatment with cabozantinib was more effective than treatment with axitinib or everolimus but was associated with higher total costs. When compared with nivolumab, cabozantinib represents an efficient option with nominally better efficacy and lower costs.
183	Cost Effectiveness of Nivolumab in Advanced Renal Cell Carcinoma.; Sarfaty M.; 2017; United States	**Target Population:** Second-line treatment of advanced RCC **Intervention:** Nivolumab **Comparators:** Everolimus and placebo	**Perspective:** Payer **Time Horizon:** 10 years **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY to $150,000/QALY **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Markov Model	**Effect:** Nivolumab generated a gain of 0.24 LYs (0.34 QALYs) compared to everolimus. **Cost:** The total mean cost per patient was $101 070 for nivolumab and $50 935 for everolimus.	**ICER/ICUR:** $146 532/QALY versus everolimus and $226 197/QALY versus placebo. Limiting the maximal treatment duration of nivolumab to 2 yr reduced the ICER to $121 788/QALY versus everolimus **Main conclusion:** Our analysis established that with a willingness-to-pay threshold of $100 000 to $150 000 per QALY, nivolumab is estimated to be cost-effective versus everolimus, but not cost-effective versus placebo.
184	Economic evaluation of nivolumab as a second-line treatment for advanced renal cell carcinoma from US and Chinese perspectives; Wan XM.; 2017; United States and China	**Target Population:** second-line treatment of mRCC **Intervention:** Nivolumab **Comparators:** Everolimus	**Perspective:** Payer **Time Horizon:** Lifetime **Parameter Sources:** Database, published studies and clinical trials **WTP threshold:** $100,000/QALY (US) and $22,785/QALY (China) **Cost type:** Direct medical costs **Discount Rates:** 3%/year **Approach:** Partitioned Survival Model	**Effect:** Patients receiving nivolumab gained 1.786 QALYs; this value was 0.29 QALYs more than that for patients receiving everolimus. **Cost:** In the United States, the use of nivolumab cost an additional $44,002.	**ICER/ICUR:** $151,676/QALY (US). For China, when nivolumab cost less than $7.90 or $9.70/mg, $22,785/QALY or $48,838/QALY, respectively. **Main conclusion:** For the United States, nivolumab is unlikely to be a high-value treatment for mRCC at the current price, and a price reduction appears to be justified. In China, value-based prices for nivolumab are $7.90 and $9.70/mg for the country and Beijing City, respectively. This study could and should inform the multilateral drug-price negotiations in China that may be upcoming for nivolumab.